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SOME OBSERVATIONS ON THE EFFECTS OF ANOXEMIA ON THE RESPIRATORY CENTER IN DECEREBRATE ANIMALS

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After section of the mesencephalon just in front of the posterior corpora quadrigemina in cats the majority of the preparations continue to breathe with perfect regularity for a considerable number of hours provided the body temperature be maintained. A certain number develop hyperpnea (1), which becomes progressively more and more marked and finally ends in convulsions, vomiting and death. In the former group of animals the CO_2 of the alveolar air and the carbonates of the arterial blood remain constant, whereas in the latter both of these values gradually decline.

The decerebrate preparations exhibiting normal breathing are most useful for the investigation of the functions of the respiratory center because this is not dulled by anesthesia, and the influence of the higher centers is removed. By the use of such preparations R. W. Scott (2), working in the laboratory of one of us (J. J. R. M.) has shown, by using a rebreathing apparatus, that there is a close correspondence between the percentage of CO_2 in the inspired air and the degree of increase in pulmonary ventilation, and that the carbonates and the C_H of the arterial blood become increased. Although at first sight the results might appear to confirm the usually accepted hypothesis that changes in the hydrogen ion concentration of the blood supplying the respiratory center constitute the sole respiratory hormone, this was shown not to be the case, since breathing atmospheres containing CO_2 still caused hyperpnea in animals that had been injected with an amount of sodium

carbonate sufficient to maintain the arterial blood well on the alkaline side of neutrality even when excess of CO_2 was being inspired (3). It was also found that if a 5 per cent solution of sodium carbonate was slowly injected intravenously (at the rate of 1 cc. per minute) the breathing remained unchanged, although P_H rose from the normal of 7.45 to 7.8 or 7.9. It was only when large amounts (over 0.35 gm. per kgm.) of Na_2CO_3 were injected that apnea occurred. By comparison of the quantitative relationship between the percentage of CO_2 in the inspired air and the volume of respired air in normal and "alkalinized" (decerebrate) animals it was found, however, that the former were decidedly more sensitive to the CO_2. It was concluded that while the respiratory center is readily excited by increase in C_H of the blood it is also responsive to an independent increase in the carbonate content. It is possible, as has been suggested by Jacobs (4), that this action is dependent upon a quicker penetration of the cells of the center by molecules of CO_2 or H_2CO_3 than by other acid radicles, and that the effective stimulus is really after all the H-ion. Whether or not this is the case, the fact remains that increase in the bicarbonate content of the arterial blood, independently of increase in C_H beyond the point of neutrality is capable of exciting the respiratory center.

The next step in the analysis of the blood changes capable of exciting the respiratory center was naturally to investigate the influence of oxygen deficiency (anoxemia) and it is this aspect of the question that is dealt with in the present investigation. At the time the work was started (1918) it was the common belief that the accumulation of acid substances possibly in the cells of the respiratory center is the fundamental cause for its excitement under these conditions, this view being that which had been set forth by Haldane and his co-workers in numerous papers (5). It is now admitted by this school (6) that oxygen deficiency *per se* acts as a stimulus on the respiratory center and the results of the present investigation corroborate this view.

METHODS

The tracheal cannula was connected with a closed system of wide-bore tubes in the course of which were inserted quickly-acting and air-tight valves, soda lime bottles and a recording Gad-Krogh spirometer, the movements of which were inscribed on a blackened surface. Several records of the rate and volume of normal breathing were first of all taken by connecting the tube beyond the expiration valve directly

with the spirometer, so that with the inspiration tube open and the outlet tube of the spirometer closed, the latter became filled with air. From the time it took for the spirometer to attain a certain level (750 cc.) the volume of normal breathing could readily be estimated, for it corresponds to the distance between the points at which the tracing leaves and regains the base line, *minus* the time required for the spirometer to empty itself, and which is indicated by the vertical line marked *a*, figure 1. Records of this type were taken every ten minutes throughout the experiments unless when the effects of anoxemia were being observed. In bringing about anoxemia the spirometer was first of all allowed almost to fill to its capacity with expired air after this had passed through the soda-lime bottle, and, the clamp being removed from the outlet tube of the spirometer, this was connected with the inspiration tube of the valve. The writing style of the spirometer now moved up and down with every respiration and the minute volume could be determined by multiplying the rate into the volume of each breath. To facilitate these measurements the tracing was calibrated by drawing horizontal lines, each representing 50 cc. The methods used for measuring the minute volumes, before and during the anoxemia periods, were therefore somewhat different in principle. The results were not exactly the same, the difference being due, we believe, partly to the somewhat greater interference with the freedom of movement of the inspired air within the closed system of tubes and partly to inertia of the spirometer. The difference was usually not significant when the tubing contained abundance of oxygen. When, on the other hand the anoxemia was acute, as when the system of tubing was partly filled with nitrogen before causing the animal to breathe into it, the volumes as calculated from the up and down movements were considerably greater than those calculated from the rate of filling of the spirometer.

At periods, both preceding and during the anoxemia, samples of alveolar air were collected by the method described elsewhere (1) and analyzed for CO_2 and O_2. Samples of air taken from the tubing beyond the spirometer were also analyzed for oxygen, so that the respiratory quotient might be determined, this value being of importance to show whether CO_2 is being given off into the alveolar air at a greater rate than O_2 is being absorbed. Under ordinary conditions the analyses of these samples were carried out by the Haldane apparatus, but in cases in which the tubing was filled with oxygen to start with the apparatus of Brodie was employed.

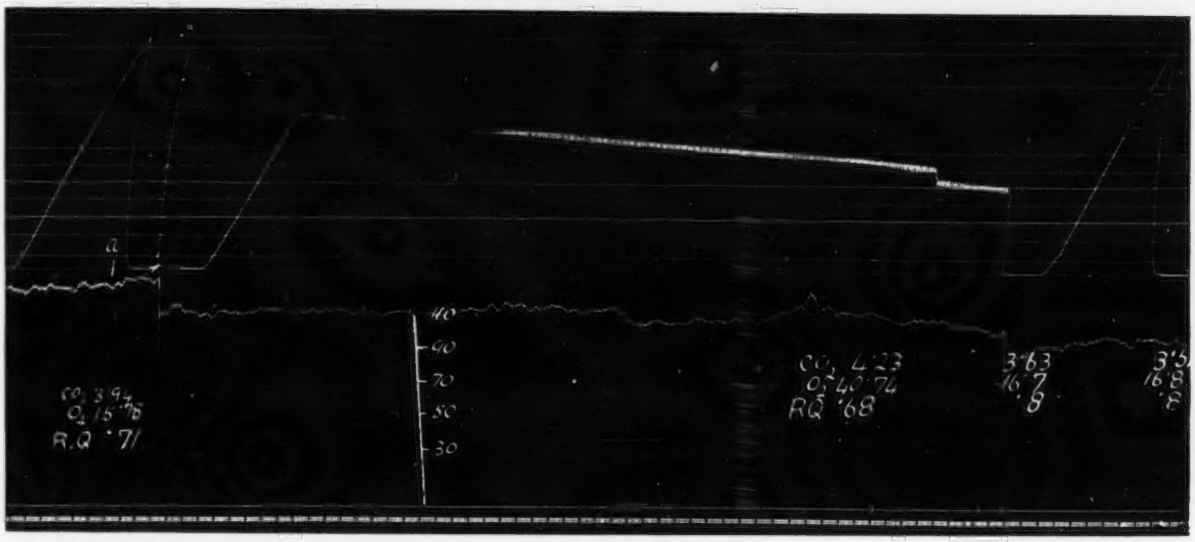

Fig. 1. Tracing showing the rate of filling of the spirometer before and after breathing into a closed system containing an excess of oxygen, and the rate and depth of breathing while the animal was thus connected. The distances between the horizontal lines equal 50 cc. The figures give the analysis of alveolar air. Time in seconds.

Portions of arterial blood were also removed for determination of CO_2 (by the Barcroft-Haldane apparatus) and for P_H (by the colorimetric method after dialysis through collodion sacs).

The arterial blood pressure was also recorded, and the rectal temperature noted from time to time.

RESULTS

These are collected in the accompanying table, in which they are grouped in each experiment for periods preceding, during and following the anoxemia. It will be convenient to consider in each of the periods, first the volume and rate of respiration, then the composition of the alveolar air, and finally the percentage of carbon dioxide.

Period preceding the anoxemia. The minute volume of respired air varied in the different preparations between 830 cc. and 1530 cc., the variations not being proportional to the weight of the animal or to the body temperature. As one of us has shown in a previous paper (1), this variability is common in decerebrate cats and probably indicates unequal degrees of excitability of the isolated respiratory center. Our impression is that the larger volumes are obtained in those animals in which decerebrate rigidity is most marked. Unequal though the volume may be for different animals, it is satisfactorily constant (in the recorded experiments) during the various periods at which it was measured. When the measurements were unequal to any decided degree, the experiment was not further continued.

The values recorded in the table are those for intervals of twenty minutes when, as a rule, the samples of alveolar air were also removed, either immediately before or after taking the records of volume.

The alveolar CO_2 in experiments 24 and 29 diminished rather rapidly, and was associated with a high minute volume of respiration. In general the alveolar CO_2 and the minute volume of respired air vary inversely to each other. In experiments not included in the present paper and in which the respiratory center was either excited or depressed by the intravenous injection of acid or alkali, respectively, the above mentioned relationship between alveolar CO_2 and respiratory volume was found to be very close.

The average respiratory quotients varied from about 0.7 to 1.00, being between 0.70 and 0.82 in eight out of the ten experiments. This is taken to indicate that the metabolism of the animals was of the normal type and that the breathing was competent to establish the normal ratio between the intake of oxygen and the output of CO_2.

The percentage of carbon dioxide in the arterial blood varied somewhat in different animals, but was tolerably constant for each one, thus making it of value to serve as an indicator of the acid-combining power of the blood. Since arterial blood was employed it was unnecessary to expose it before analysis to an atmosphere containing a known per-

TABLE 1

NUMBER OF EXPERIMENT	SEX	WEIGHT	CONDITION OF ANIMAL. DURATION OF ANOXEMIA	RESPIRATIONS		O_2 IN INSPIRED AIR	ALVEOLAR AIR			BLOOD CO_2
				Rate per minute	Minute volume		CO_2	O_2	R. Q.	
		kgm.			*cc.*	*per cent*	*per cent*	*per cent*		*per cent*
X	♀	2.5	Normal	60		20.96	2.44	17.77	0.71	
			Anox. 10 min.	60			1.81	11.83	1.81	
			Normal			20.96	2.76	17.43	0.72	
			Normal			20.96	2.29	18.0	0.71	
XXII	♂	2.8	Normal		920	20.96	2.93	17.15	0.90	47.0
			Normal		850	20.96	2.09*	18.92	1.04	
			Anox.				1.97	16.3		
			Anox. 26 min.			14.2	2.77	12.05	1.32	41.0
XXIII	♀	3.4	Normal		1020	20.96	3.52	16.4	0.72	45.3
			Normal		920	20.96	3.65	16.1	0.70	44.8
			Anox.	29	1120	14.25	3.08	12.4	1.89	38.8
			Anox. 15 min.	34	2040	7.7	2.05	6.8	2.87	
			Normal		1650	20.96	2.43	18.15	0.83	37.8
										38.4
XXIV	♀	2.1	Normal	36	1220	20.96	3.95	16.6	0.89	
			Normal		1350	20.96	3.78	16.1	0.77	
			Normal		1340	20.96	3.53	16.6	0.81	35.37
			Normal		1530	20.96	3.21	17.2	0.82	38.04
			Anox.	40	1845	16.3	3.06	14.4	1.63	
			Anox. 12 min.	39	2300	10.3	2.42	9.28	2.36	
			Normal			20.96	2.70			
			Normal		1630	20.96	2.71	18.1	0.95	38.04
XXV			Normal	24	1070	20.96	3.12	16.85	0.71	29.6
			Normal		1500	20.96	2.79	17.15	0.68	28.7
			Anox.		*2900†	10.95	2.08	8.65	0.79	29.6
			Anox.		4000					
			Anox. 8 min.		1920					
			Normal		1800	20.96	1.94	18.35	0.69	21.6

TABLE 1—*Continued*

NUMBER OF EXPERIMENT	SEX	WEIGHT	CONDITION OF ANIMAL. DURATION OF ANOXEMIA	RESPIRATIONS		O_2 IN INSPIRED AIR	ALVEOLAR AIR			BLOOD CO_2
				Rate per minute	Minute volume		CO_2	O_2	R. Q.	
		kgm.			*cc.*	*per cent*	*per cent*	*per cent*		*per cent*
			Normal		830	20.96	3.55	16.75	0.81	27.0
			Normal		905	20.96	3.41	16.55	0.72	29.1
XXVI	♂	4.0	Normal		905	20.96	3.21	17.28	0.85	32.9
			Anox.		2160	17.3	2.42	15.25	1.02	29.7
			Anox. 11 min.		2870	11.12	2.20	9.67	1.35	30.24
			Normal		1800	20.96	1.12	20.25	1.09	22.7
				#						18.9
		†								
			Normal			20.96	3.41			35.18
			Normal			20.96	3.39	16.73	0.84	
			Normal			20.96	3.14	16.75	0.69	
			Normal			20.96	3.10	16.80	0.69	35.10
XXVIII	♀	2.0	Anox.	31	1350	17.00	2.43	15.34	1.58	37.8
			Anox.	30	1250	15.4	2.18	12.95	0.8	
			Anox. 25 min.	31	1400	7.36	1.67	5.84	1.09	37.8
			Normal			20.96	1.35	19.65	1.05	
			Normal	40	1120	20.96	3.08	17.85	0.99	51.8
			Normal			20.96	2.79	17.80	0.85	
			Normal			20.96	2.11	18.55	0.84	51.3
XXIX	♀	2.0	Anox.	50	1700‡	19.5	2.14	17.7	1.27	41.5
			Anox.		2250					
			Anox.	60	2700	16.2	2.00	14.55	1.33	
			Anox.	60		9.2	2.17	8.12	2.4	37.5
			Anox. 14 min.		1620					
			Normal	30	840	20.96	3.11	17.38	0.83	
			Normal			20.96	3.32	16.3	0.66	
			Normal	20	760	20.96	3.27	16.5	0.68	
XXXVII	♀	1.75	Anox.**		1320§		2.21	8.4	1.2	
			Anox.**	38	1900					
			Anox.** 8 min.		Great decrease					
			Normal		700	20.96	1.77	19.2	0.99	
			Normal				2.28	18.2	0.78	

TABLE 1—*Concluded*

NUMBER OF EXPERIMENT	SEX	WEIGHT	CONDITION OF ANIMAL. DURATION OF ANOXEMIA	RESPIRATIONS		O_2 IN INSPIRED AIR	ALVEOLAR AIR			BLOOD CO_2
				Rate per minute	Minute volume		CO_2	O_2	R. Q.	
		kgm.			*cc.*	*per cent*	*per cent*	*per cent*	*per cent*	*per cent*
			Normal	20	680	20.96	3.76	16.97	0.92	
			Normal		600	20.96	4.11	16.05	0.80	
			Normal		780	20.96	4.05	16.00	0.78	
			Normal		680	20.96	3.64	16.20	0.75	
			Anox.‡‡	30	960††					
XXXVIII	♀	2.1	Anox.‡‡	32	1120	11.5	3.32	8.1	0.92	
			Anox.‡‡		1080	9.9	2.80	7.68	1.23	
			Anox.‡‡ 13 min.		770		3.32	3.52	1.00	
			Normal			20.96	2.91	17.6	0.83	
			Normal			20.96	2.90	17.8	0.89	
			Normal			20.96	2.78	18.2	1.00	

X. Blood pressure 140 mm. unaffected by anoxemia.
During a second period of anoxemia there was marked periodicity.

XXII. Body temperature 34°C.
* Low result probably due to a period of hyperpnea.

XXIII. Blood pressure remained unchanged (at 90 mm.) during anoxemia.

XXIV. Blood pressure 120 mm. at beginning of anoxemia and 105 mm. at end.
During a second period of anoxemia, hyperpnea developed early but breathing soon failed.

XXV. System filled with air and nitrogen before connecting animal with it. Blood pressure rose from 80 to 130 mm. Hg. and oscillated greatly.
† Calculated from first breath after lever came to top. Extreme hyperpnea soon followed by failure of the respiratory center. Periodicity very distinct.

XXVIII. After initial increase, the breathing scarcely changed during the anoxemia. The blood pressure rose from 75 to 90 mm. during anoxemia. O_2 used at rate of 225 cc. per minute at 15.3 per cent O_2 alveolar air, and at 20 cc. per minute at 6 per cent O_2 in alveolar air.

XXIX. ‡ Calculated from first breath after lever came to top.
O_2 used at rate of 26 cc. per minute at 15 per cent O_2 in alveolar air, and at 17 cc. per minute at 8 per cent O_2 in alveolar air.

XXXVII. § Calculated from first breath after lever came to top.
** Nitrogen added to air of rebreathing apparatus.

XXXVIII. Blood pressure did not change during anoxemia.
†† Calculated from first breath after lever came to top.
‡‡ Nitrogen added to air of rebreathing apparatus.

centage of CO_2, as recommended for venous blood by Van Slyke. In the few experiments in which it was possible to obtain satisfactory measurement of P_H this value stood at 7.4 or 7.45.

Period during the anoxemia. The behavior of different animals when exposed to gradually decreasing percentages of oxygen was not precisely the same. Some of them were able to withstand much longer periods of anoxemia than others, as judged by indications of respiratory break-down, rise in blood pressure and the appearance of Traube-Hering curves. The average duration of the anoxemia period, starting with air in the tubing, was thirteen minutes, but one animal (no. 28) could be continued for twenty-five minutes without any unfavorable symptoms supervening. In this animal the respirations were stimulated early in the experiment, but thereafter they scarcely became changed, even when the percentage of oxygen in the alveolar air had fallen to about 6. There was a gradual rise in arterial blood pressure during the anoxemia. We are at a loss to explain the results of this experiment.

With reference to the effects of oxygen deficiency on respiratory volume, it is difficult to say at precisely what percentage of alveolar oxygen distinct increase occurred in these experiments. It was decided at a percentage of 15.25 (no. 26) and became progressively more and more marked as the percentage fell below this value. At percentages of alveolar oxygen between 8.1 and 9.3 in four experiments (24, 25, 37 and 38) the percentile increase over the normal volume of breathing varied between 50 and 170. The difficulty in determining the precise percentage of oxygen at which increased breathing supervenes is due to the fact that a certain degree of this occurs shortly after the animal has been connected with the closed system of tubes. The slight resistance to the movement of the air probably causes a greater degree of alteration in intra-alveolar pressure and consequently a stimulation of afferent respiratory fibers.

The foregoing results are obtained from the record of the respirometer, but a still more valable indicator of hyperpnea is afforded by examination of *the alveolar CO_2 and the respiratory quotient.* The increased ventilation of the alveoli causes both the percentage of CO_2 added to the air and the percentage of oxygen removed from it to become decreased, but the former to a lesser degree than the latter, since the blood cannot absorb oxygen beyond its carrying limits for this gas, whereas the CO_2 is blown off in proportion to the degree of ventilation of the alveoli. As judged by this criterion, evidence of stimu-

lation of the respiratory center was obtained when the alveolar oxygen stood at 17.7 (no. 29), 15.34 (no. 28) and 15.25 (no. 26), the oxygen percentages in the inspired air in these experiments being 19.5, 17 and 17.3 respectively.

In one animal (29), therefore, both the tracings and the respiratory quotient indicated a decided degree of hyperpnea when the percentage of oxygen in the inspired air had fallen only to 19.5 and by the time it

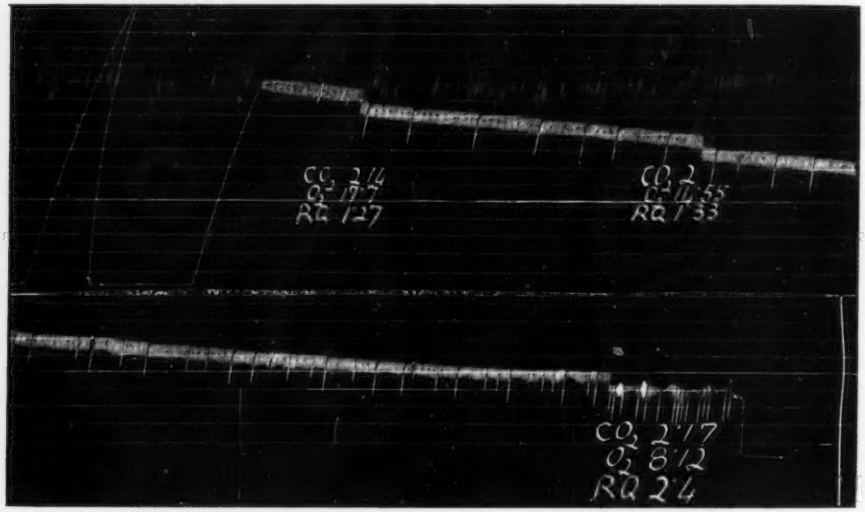

Fig. 2. Tracing of respiration during the gradual development of anoxemia (exper. 29). The figures give the percentage composition of the alveolar air, the sudden falls of the tracing being due to the removal of samples of air from the closed system. To conserve space, the tracing has been cut in the middle, the second portion being placed under the first. Time in seconds.

had reached 16.2 per cent not only was the depth of each breath greatly increased, but there was decided acceleration in the rate of breathing. This tracing is shown in figure 2.

As the percentage of oxygen declines the breathing becomes more and more excited until it reaches an optimum beyond which it rapidly becomes less, indicating exhaustion of the respiratory center. The exact percentage of oxygen, at which this breakdown of the center occurs, no doubt varies according to whether the observation was started

with air or a mixture of oxygen and nitrogen in the tubing. In the experiments in which mixtures containing about 8 per cent of oxygen were employed to start with (25, 37 and 38) the breathing quickly became much greater, and was followed within a few minutes by a marked slowing, and later also by a decrease in amplitude (fig. 3). Commonly also, as will be described more in detail in another paper,

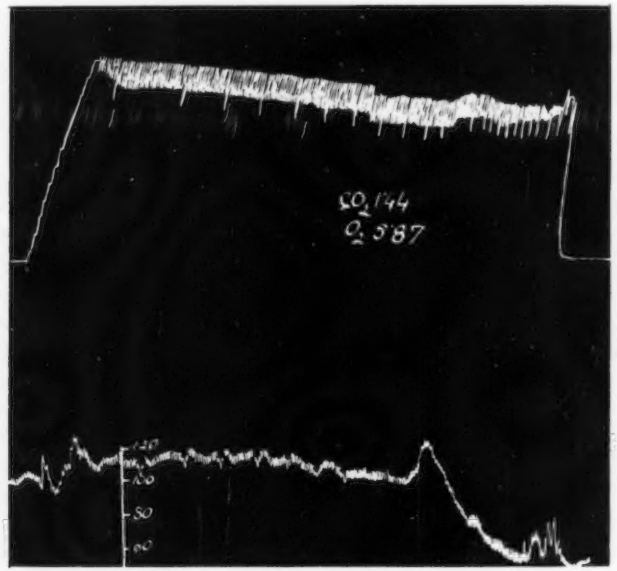

Fig. 3. Tracings of breathing, taken with spirometer, when the inspired air contained about 8 per cent of oxygen to start with. The arterial blood pressure is also shown (exper. 25).

periodicity in breathing became evident in these experiments, and deep gasps made their appearance with progressively increasing frequency. The depressing effects of oxygen deficiency appeared when the alveolar oxygen had fallen to between six and eight in the three experiments (25, 37 and 38) in which an oxygen-poor atmosphere was breathed from the start. In two other experiments (23 and 28) in which the onset of the anoxemia was gradual there was no evidence of exhaustion of respiration even at 6 per cent. All our experiments show that the

failure of the breathing, once it sets in, progresses very quickly to complete apnea, and is accompanied by a rise in arterial blood pressure. With regard to the rate of breathing it will be observed that only a slight degree of quickening usually occurred, the increased minute volume being due almost entirely to increased depth.

The rate of oxygen consumption can be estimated from the tracings by measurement of the time taken for the mean of the respiratory tracing to descend through a distance corresponding to 50 cc. In two animals of the same size (2 kgm.) (29 and 28) this was found to be 26 cc. per minute and 22.5 cc. per minute (or 13 and 11.25 cc. per kilo body weight) when there was an adequate percentage of oxygen and 8.5 and 10 cc. respectively when the oxygen was reduced below 8 per cent.

All the above evidence goes to show that the oxygen of the alveolar air cannot as a rule be reduced much below 8 per cent in decerebrate cats without a breakdown of the respiratory function and an inadequate assimilation of oxygen. It should be emphasized, however, that all animals do not behave exactly alike in this regard.

It will be convenient to defer consideration of the behavior of the CO_2 content of the blood until the *after-effects* of the anoxemia have been studied. These were particularly investigated in experiments 10, 23, 24, 25, 28, 37 and 38, the intervals of observation in each case being twenty minutes, as before. It will be observed that the respiratory volume did not usually return quite to the normal level immediately following the anoxemia, although the respiratory quotient fell markedly except in experiment 28, in which it remained high. With the exception of experiments 23 and 24, the percentage of CO_2 in the alveolar air was lower than during the anoxemia period. Since the volume of air respired was less, this must indicate that CO_2 was being retained by the blood to make up for the excess that had been blown off during the hyperpnea. The concomitant reduction in the respiratory quotient is due to the fact that oxygen absorption was less active than it had been in the normal period preceding the establishment of the anoxemia. Evidence is therefore furnished to show that the animals did not return to a perfectly normal condition after breathing deficiency of oxygen, and this was further shown by the fact that in nearly every case in which anoxemia was induced a second time in the same animals, the respiratory center broke down early, and the experiment had to be terminated to save the animal.

The temporary inadequacy of oxygen supply definitely depresses the power of decerebrate cats to withstand a second period of anoxemia, and further evidence that permanent damage is done is afforded by the tendency to periodic breathing, Traube-Hering oscillations of blood pressure and frequent movements of the head and extremities.

Turning now to *the CO_2 content of the blood*, a marked reduction occurred during anoxemia in only one of the experiments (no. 29), a slight reduction in three (nos. 22, 23 and 26) and it remained practically constant, in two (nos. 25 and 28). These estimations were made in duplicate, and there is no doubt as to the reliability of the figures. We expected a decided reduction because of the hyperpnea, and that this did not always occur is probably due to the fact that the hyperpnea was not of sufficient degree, or duration, to produce a measureable effect on the bicarbonate reserves of the blood and tissues. A more definite reduction in blood carbonate was observed in three experiments (23, 26 and 25), in which the estimations were made *after* the animal had respired outside air subsequent to the anoxemia period. Although, as one of us has shown elsewhere, a certain decrease in blood carbonate occurs in many decerebrate cats without any anoxemia, the decrease in the present experiments is much greater than would be expected within equal periods of time even had these been on animals belonging to this group and it indicates that CO_2 had been blown off from the blood as a result of the hyperpnea.

P_H of the blood was measured in several of the experiments, but the results were not of such a nature that we can say definitely whether there was any change. In one case (no. x) there was a perceptible increase in this value.

The blood pressure remained practically constant in all of the experiments until the O_2 in the alveolar air fell to about 7 per cent, when it usually rose and became periodic in character. With further reduction in oxygen the blood pressure fell rapidly, and in the great majority of the observations the experiment was terminated at this stage.

Although we have not succeeded in obtaining results that are as constant as we had hoped for, several definite conclusions are warrantable. Before we draw these, however, it must be pointed out that the investigation was started at a time (November, 1918) when the current belief was that stimulation of the respiratory center during anoxemia is due to the appearance in the organism, and particularly in the nerve centers, of unoxidized organic acids, and that it was only after a large

part of the experiments had been completed that Haldane, Y. Henderson and others showed this hypothesis to be untenable. The early onset of hyperpnea in our experiments, as judged both from the tracings and the behavior of the respiratory quotient led us to conclude that respiratory stimulation in conditions of anoxemia occurred at a much higher percentage of oxygen and much earlier in the anoxemia period than could be accounted for by the appearance of unoxidized

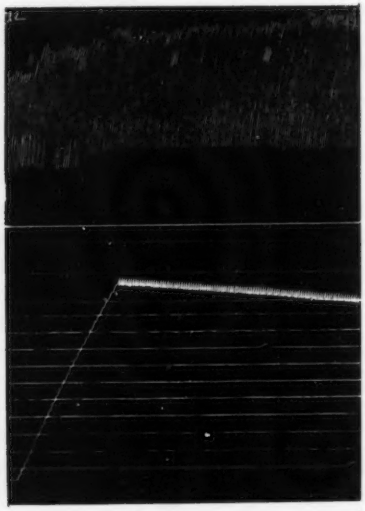

Fig. 4. Tracing of breathing taken with tambour connected with closed system in upper tracing, and with Gad-Krogh spirometer in lower tracing. The air in the system contained an excess of oxygen so that the augmentation in breathing, seen in the upper tracing must be due to mechanical factors. Time in seconds. The two upward steps in the tambour tracing are due, the first one to connecting the expiration tube with the spirometer and the second, to this connecting both inspiration and expiration tubes.

acids. These results were communicated to the American Physiological Society (7) but we did not venture to suggest that oxygen deficiency could in itself be responsible for the stimulation. We thought that the slightly greater resistance to the movement of air due to breathing into a closed system of tubes might be responsible for the hyperpnea. On subsequently testing this possibility, however, by varying the resistance to breathing, we found it to be inadequate to account for

the degree of hyperpnea that was observed. For example, we found in several experiments that stimulation of the respiratory center occurred only to a slight degree when the animal was allowed to breathe into a closed system containing an excess of oxygen. Thus, in one of the experiments the respiratory volume (per minute) before connecting with the closed system was 725 cc., R. Q., 0.71; CO_2, 4.19; and during breathing into the system these values were 850 cc., 0.68 and 4.23 respectively. In another experiment of the same character but in which the resistance was probably greater R. Q. rose from a normal of 0.70 to 1.07, but it did not rise any farther on continuing the breathing into the closed system for some time. There are indications, however, that in many of the experiments a slight degree of hyperpnea was due to this cause, because the height of the steps caused by the elevation of the spirometer with each breath became progressively greater (Cf. fig. 1 and fig. 2). The possibility of errors due to this mechanical hyperpnea has been guarded against in the figures given in the tables by taking the tracings caused by the first few breaths, after the spirometer had become filled, for the purpose of calculating the normal minute volume. Unfortunately it was impossible to control the R. Q. in the same way, but it is scarcely likely that the high values observed could have been caused by this mechanical factor alone.

We realize that because of this factor our observations are insufficient in number to permit of our stating with any precision the exact degree of oxygen deficiency which is necessary to stimulate the respiratory center, but we are certain that it occurs considerably before this has reached 17 in the inspired air, which corresponds to about 15 in that of the alveoli.

CONCLUSIONS

In decerebrate cats in which the effects of ether have entirely disappeared and the respiratory volume, alveolar CO_2 and R. Q. are constant, or only slowly falling, hyperpnea becomes evident before the percentage of oxygen in the inspired air has become reduced, by rebreathing through soda lime bottles, to 17. It has been impossible to make certain of the occurrence of hyperpnea at higher percentages of oxygen by the method employed because of the slight degree of hyperpnea which is brought about on account of the resistance offered by the system of tubing.

The hyperpnea is detected partly by measurement of the respiratory volume and partly by analysis of the alveolar air. From the results by the latter method, the decrease in the percentage of CO_2 and the marked increase in R. Q. afford evidence of greater alveolar ventilation. As the percentage of oxygen in the inspired air continues to fall the hyperpnea becomes more marked and attains an optimum at a percentage of oxygen in the inspired air which varies in different animals, but is apparently usually between 9 and 11. Below this percentage the respiratory center usually passes quickly into a depressed state, the breathing becoming at first slow and periodic in type, then very irregular both in amplitude and rate and finally ceasing altogether.

The arterial blood pressure remains unchanged until after the optimum of breathing has been reached, when it rises and usually develops marked Traube-Hering waves. It then falls rapidly. If the animal be allowed to breathe outside air before the blood pressure has fallen far, it soon recovers and for a time the breathing is usually exaggerated and may be periodic in type. The periodicity usually takes the form of deep sighs, which become more and more frequent as the percentage of oxygen declines.

If the animal be caused to breathe into the rebreathing apparatus a second time it withstands the oxygen deficiency very badly, and in the present research has usually died of respiratory failure and fall of blood pressure before any sample of alveolar air could be collected.

In several of the experiments no definite changes could be observed in the percentage of CO_2 in the arterial blood, but in others a decrease was evident. This indicates that the hyperpnea was not usually of sufficient degree, or duration, to cause the development of a marked acapnia.

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PERIODIC BREATHING AND THE EFFECTS OF OXYGEN ADMINISTRATION IN DECEREBRATE CATS

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In the course of observations on the effects produced on the breathing of decerebrate cats by reducing the percentage of oxygen in the inspired air, it was observed that periodicity often developed and that certain animals in which the breathing was inadequate to maintain life could be made to breathe normally by the administration of large quantities of oxygen. Because of the quantitative determinations which it was necessary to make in the earlier experiments (1) it was impossible to investigate these two interesting phenomena more thoroughly, but this has been done in subsequent experiments, and the following is an account of the results so far obtained.

The cats after being placed deeply under ether were decerebrated by means of the guillotine of Sherrington, and were then left on a warmed table for about an hour so that all traces of ether might be removed from the body. The tracheal cannula was then connected with wide-bore tubing and records of the breathing obtained by means of tambours or a Gad-Krogh spirometer. The arterial blood pressure was also recorded.

PERIODIC BREATHING

This could be induced in a variety of ways, but the susceptibility of different animals to exhibit it was found to vary considerably. Certain of them breathed spasmodically from the start but without any regular periodicity of the Cheyne-Stokes type, and it was in certain of these that administration of oxygen was found to bring about regular breathing. Many breathed with perfect regularity at the start but developed a slight degree of permanent regular periodicity after being caused to breathe in atmospheres containing a low percentage of oxygen. In these preparations marked periodicity could readily be established by practically any of the methods about to be described. In a few cats

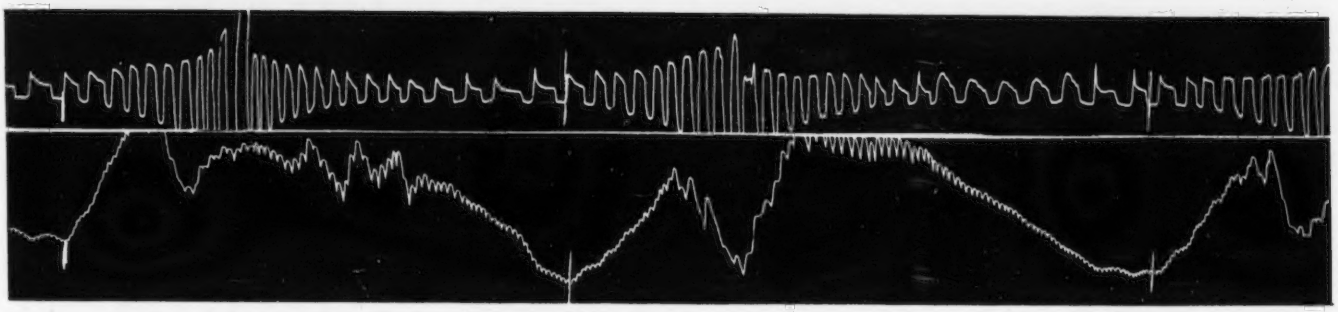

Fig. 1. Tracings of the respirations and arterial blood pressure during periodic compression of the vertebral arteries. The compression was applied at the vertical marks and lasted to about the greatest excursion of the respiratory tracing.

the breathing could not be caused to alter from the regular type except when the oxygen was greatly reduced, when it became irregular with frequent gasps without, however, exhibiting any Cheyne-Stokes rhythm.

The methods employed to bring about the periodicity were in general the same as those described by Douglas and Haldane (2) in observations on man, and it will be observed that in all of them a deficiency of oxygen can be shown to be the ultimate cause of the condition.

The following results were obtained:—

1. Periodic digital compression of the vertebral arteries, below the transverse processes of the atlas (fig. 1). Immediately after the compression, the breathing became increased in frequency and depth and the arterial blood pressure rose. It was not possible to mark precisely the moment at which the vertebral arteries were effectively occluded, but this corresponded very closely to the vertical lines on the tracing. It will be observed that the rise in blood pressure sets in before the respirations become perceptibly augmented. This relationship could readily be confirmed by observation of the movements of the writing levers during the compression, and it indicates that the vasoconstrictor center is stimulated by the curtailment of blood flow before the respiratory. No doubt the continued rise in blood pressure is due in part to increased activity of the respiratory pump, but the rise starts before this can have come into play. The blood pressure continues to mount rapidly, the respirations also becoming progressively more frequent and deep, until a stage is reached at which the pressure suddenly falls, although the hyperpnea is becoming more marked. This fall is due to stimulation of the vagus center, which, however, soon diminishes in intensity, so that, although still decidedly slowed, the heart now recovers sufficiently in rate to allow the rise in blood pressure to continue. After removal of the compression the breathing rapidly declines, but the blood pressure remains elevated for some time with decided slowing of the pulse. The conclusion which may be drawn is that curtailment of blood flow to the medulla causes stimulation first, of the vasoconstrictor center, then of the respiratory center, and finally of the vagus center.

2. Breathing into a small flask containing soda lime. The capacity of the tubing and flask including the soda lime, beyond the trachea was approximately 120 cc., but it had to be altered somewhat in different observations in order to maintain the maximal degree of periodicity. Figure 2 shows typical results obtained by this method. It will be observed that it is the depth, rather than the rhythm of the respira-

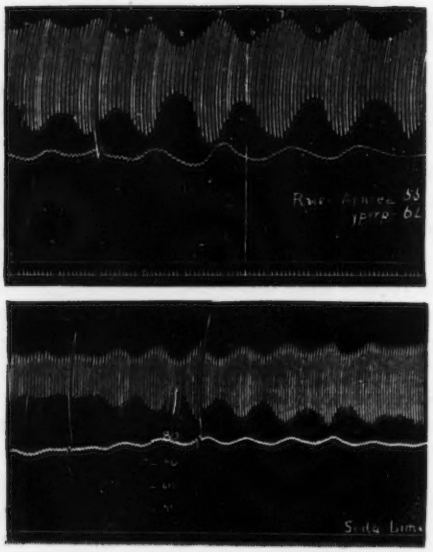

Fig. 2. Tracings of the respirations and arterial blood pressure during breathing into a tube and flask containing soda lime. Time in seconds.

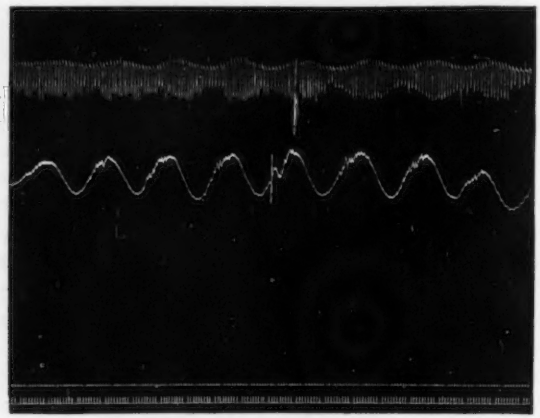

Fig. 3. Tracings of the respirations and arterial blood pressure during breathing into a tube and flask containing soda lime after the animal had been respiring in an oxygen-poor atmosphere. The important features of this tracing are that it shows a more marked periodicity of blood pressure than of respiration and evidence of vagus slowing of the heart as the blood pressure rises during each period. Time in seconds.

tions that becomes stimulated during the hyperpneic periods. The explanation for the development of the periodicity is, as Haldane has pointed out, that the percentage of oxygen becomes gradually used up because the animal, while breathing quietly, reinspires the column of air contained in the tubing and bottle. The oxygen deficiency stimulates the respiratory center with the result that outside air is drawn into the tubing and the oxygen deficiency removed, so that the breathing returns toward the normal. It is difficult to say whether the oscillations in arterial blood pressure are merely secondary to the greater activity of the respiratory pump. So far as we have been able to observe, such is the case, but we have not succeeded in experiments of this type on animals that were breathing with perfect regularity before

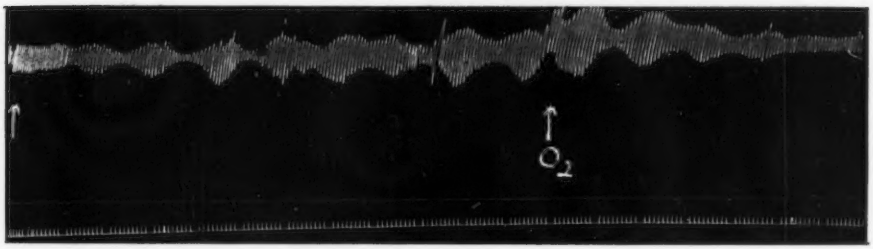

Fig. 4. Tracing of respiration after connecting the trachea with a tube 400 mm. long. At the second arrow O_2 was introduced into the trachea.

being connected with the soda lime apparatus, to detect any slowing of the heart. In animals in which a certain degree of periodicity already existed as a result of previously breathing air deficient in oxygen, however, evidence of a certain degree of stimulation of the inhibitory center was sometimes obtained (see fig. 3). The first part of this tracing (fig. 3) also exhibits marked periodicity in the blood pressure curve with practically regular breathing. This was not infrequently observed expecially in animals after they had been caused for some time to breathe in atmospheres containing a deficiency of oxygen.

3. Increasing the dead space by connecting the tracheal cannula with a piece of rubber tubing (fig. 4). A tube of 10 mm. bore and 400 mm. long usually gave the best results, and it should be pointed out that only a few cats developed any periodicity by this method. Introduction of oxygen into the trachea by catheter immediately restored normal breathing. The observation is of interest since, as pointed out by

Haldane, it duplicates the essential conditions which are responsible for periodic breathing in hibernating animals. In these the gaseous metabolism being greatly diminished, the dead space becomes relatively so far increased that no outside air enters the alveoli during quiet breathing. The oxygen thus becomes used up and the respirations sufficiently stimulated for outside air to enter the alveoli and remove the anoxemia.

4. During or after breathing in atmospheres containing a deficiency of oxygen. In experiments described elsewhere (1) in which a state of anoxemia was brought about by causing animals to respire into a closed system containing soda lime it was frequently observed that the breathing became periodic as the percentage of oxygen declined. The exact percentage of alveolar oxygen at which this appeared varied for different animals, but it was usually below 12, and the periodicity became more marked as the percentage fell to about 8. At lower percentages failure of respiration usually set in. The first indication of periodicity in such cases was the occurrence of deep sighs, the intervals between which gradually lessened as the anoxemia became more intense. Immediately following each sigh the breathing was much less than before, and it gradually increased to a maximum, and then fell off again, this being repeated with more or less regular periodicity until the next sigh. After restoring the animals to outside air many of them breathed regularly, but in a considerable number periodicity of a mild degree was maintained and could readily be made more marked by slightly decreasing the percentage of oxygen in the respired air (fig. 5).

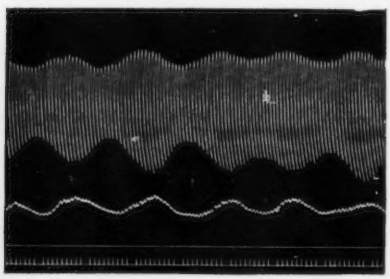

Fig. 5. Tracings of respirations and arterial blood pressure in an atmosphere containing 18.5 per cent O_2 after a period of acute anoxemia. Time in seconds.

Several other methods were tried to induce periodic breathing, such as slight maintained curtailment in the blood supply to the medulla, or the application of local heat and cold, but without success. So far as our results go, they show that moderate deficiency in oxygen supply is the essential cause for the condition, and it is probable that by drugs, or in other ways, the threshold of excitability of the respira-

tory center could be altered so that periodicity in its action would supervene without alteration in the average level of oxygen tension in the blood circulating in it. The varying susceptibility of different cats to develop periodic breathing under the above described conditions is worthy of emphasis, since a similar variability is seen in the case of man. We do not know whether the exact position of the cut is an important factor in this connection. As has been pointed out by Marckwald section of the brain stem just above the medulla is a frequent cause for a peculiar type of periodic breathing in rabbits (3).

RESTORATION OF THE REGULAR ACTION OF THE RESPIRATORY CENTER BY INCREASING THE OXYGEN TENSION OF THE ALVEOLAR AIR

As has been shown elsewhere, decerebration is not always followed by the same results, the differences being dependent partly on the age of the animal and partly on the exact position at which the mesencephalon is cut. Besides the animals which continue to breathe in normal fashion and without any apparent disturbance in the acid-base equilibrium of the body, there are two other groups. In one of these the breathing, although normal at first, becomes in a couple of hours or so, hyperpneic, and marked disturbances in the acid-base equilibrium become evident (4). In the other group the breathing is irregular and spasmodic from the start and the animals soon develop the symptoms of asphyxia with convulsive movements which terminate in death. It has been found that several, although not all, of the animals of this last group react in a remarkable way toward the administration of oxygen, the breathing becoming regular and the preparation normal in every other respect (reflexes, etc.). Tracings of the breathing in one of these animals are given in figure 6. The breathing in this preparation was so inadequate from the start that to maintain life the respiratory pump had to be used, the effect of which is seen at the beginning of tracing I. On discontinuing the pump, the breathing was somewhat improved. A catheter was then passed into the trachea so that its end lay at the bifurcation, and oxygen gas was allowed to enter the trachea freely. In about 5 minutes the breathing became regular and gradually increased in frequency until in about 10 minutes after starting the oxygen it was proceeding at the rate of 14 to 15 the minute. Discontinuance of the oxygen was followed by a period averaging about 10 minutes during which the breathing remained normal, but then it became slow and irregular and ultimately assumed its old type as

shown in tracing IV. Readministration of oxygen again restored the breathing to normal. These observations could be repeated indefinitely.

It should be stated further that in the animal from which the above tracings are taken and in others which reacted similarly to oxygen the arterial blood pressure was comparatively low (60 mm.).

An interesting feature of the resuscitation is the suddenness with which the breathing usually changes from the irregular to the regular type. This is well seen in tracing II. After becoming regular it may remain slow for some time, but later picks up and assumes the normal rate. It was attempted to accelerate its recovery to the normal rate

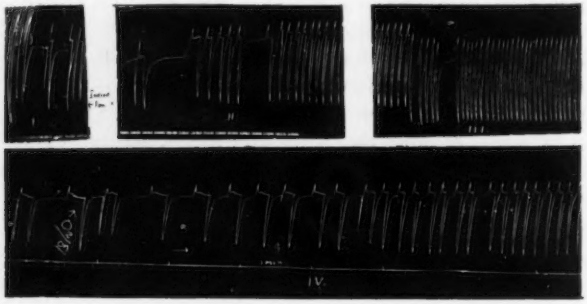

Fig. 6. Tracings of respirations in a decerebrate cat in which spontaneous breathing was so slow and irregular that symptoms of asphyxia supervened. The first part of tracing I shows the effect of artificial respiration with the pump while O_2 was being delivered into the trachea through a catheter. The pump was discontinued but the O_2 insufflation maintained and in about 5 minutes the respirations became suddenly regular as shown in tracing II. The O_2 was discontinued toward the end of tracing III and in about 10 minutes the breathing returned to the condition shown in tracing IV, in which also the effect of again giving oxygen is shown. Time in tracings I, II and III in seconds. Time in tracing IV in minutes.

by increasing the intrapulmonary pressure by placing weights on a spirometer attached to the respiration tube, but no decided improvement in breathing was observed to occur. Adding CO_2 to the inspired air excited the respirations, but did not shorten the time required for normal breathing to return.

Occasionally the beneficial effect of oxygen on the breathing persisted for considerably more than the average of 10 minutes.

These observations would appear to be of some importance in connection with oxygen therapy in man. They indicate that under certain conditions of breathing at atmospheric pressure a sufficient supply of oxygen may not be carried to the respiratory center to maintain its excitability. One cause of such a condition would be low arterial blood pressure, and it is of interest to note that this was observed to be present in the decerebrate preparations which most successfully responded to the oxygen treatment.

CONCLUSIONS

1. Periodic breathing can be induced in many decerebrate cats by the following methods: *a*, periodic compression of the vertebral arteries; *b*, respiring through a tube containing soda lime; *c*, increasing the dead space of the lungs; *d*, during or following respiration in atmospheres containing from about 8 to 12 per cent of oxygen.

2. The arterial blood pressure exhibits waves synchronous with those of the respirations, and occasionally there is evidence of vagus slowing of the heart during the rising part of the curve. The arterial waves are often relatively much more pronounced than the respiratory, and occasionally the former may be marked without any detectable periodicity of breathing.

3. In several decerebrate cats in which the respirations were very slow and irregular in rhythm and utterly inadequate to maintain life, normal breathing was established, and the preparation maintained for several hours in excellent condition, by the administration of oxygen through a catheter into the trachea.

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THE CONCENTRATION OF LACTIC ACID IN THE BLOOD IN ANOXEMIA AND SHOCK

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In conditions of anoxemia and shock it has been considered possible that certain of the symptoms are dependent upon the appearance of an excess of lactic acid in the tissues and the blood. During several years Haldane and his collaborators maintained that the stimulation of the respiratory center which occurs during life in atmospheres containing a deficiency of oxygen is caused by an increase in the H-ion concentration in the environment of the cells of the respiratory center and that this is brought about by the appearance of incompletely oxidized organic acid, which was supposed to be lactic acid (1). The demonstration by Araki (2) that excess of this acid does appear in the organism in conditions of anoxemia appears to have afforded the chief support for this view but no further evidence favoring it could be brought forward. Ryffle (4), for example, could detect only a moderate increase in the percentage of lactic acid in the blood (venous) of man after breathing for four hours in an atmosphere containing 12 per cent of oxygen and, in other observations of a similar nature, he could not detect any excess of lactic acid in the urine. Furthermore this same worker, in collaboration with Barcroft (5), was unable to detect a sufficient increase of lactic acid in the blood of persons living in rarefied air to account for the degree of lowering of the dissociation constant of oxyhemoglobin that was actually found to exist, in the absence of CO_2; nor could lactic acid be detected in the urine of these persons. The relatively slow onset and disappearance of the so-called acidosis in conditions of mountain sickness also did not conform with the view that the accumulation of lactic acid in the organism could be the responsible cause. F. H. Scott also pointed out that hyperpnea is excited by oxygen deficiency within too brief a period of time to make it probable that accumulation of lactic acid is the cause (6).

Haldane and his collaborators (3) have more recently abandoned the lactic acid hypothesis, as we may call it, in favor of the older one

that oxygen deficiency *per se* can act as a stimulus on the respiratory center, either directly or because it lowers the threshold of excitability and so allows a meanwhile unchanged normal stimulus, such as the H-ion concentration, to have a greater effect. Even granted that oxygen deficiency does have this direct effect there is no evidence that under certain conditions of anoxemia accumulation of lactic acid in the body may not also be a contributory factor to the respiratory disturbance. This could be shown only by determination of the degree of anoxemia, and the time after its establishment, that is necessary to cause a sufficient amount of lactic acid to appear in the organism to disturb the acid-base balance, and it was partly with this object in view that the present investigations on the effects of anoxemia were undertaken. It is recognized that the mere detection of an excess of lactic acid in the blood in anoxemia does not necessarily prove that it is the result of defective oxidation or that it has any relationship to the cause of the respiratory excitement. It may rather be dependent upon the condition of "alkalosis" which is brought about by a blowing-off of CO_2 from the blood in the lungs. The lactic acid in other words may be formed for the purpose of taking a share in neutralizing the relative excess of alkali. Support for the view is afforded by the fact that excess of lactic acid accumulates in the blood, and some appears in the urine, when the acid-base equilibrium is disturbed by the intravenous injection of solutions of sodium carbonate (7) or even when bicarbonate is taken with the food (8). If the appearance of lactic acid in anoxemia is entirely secondary to the establishment of an alkalosis condition it would not be expected to occur in asphyxia where the Co_2 accumulates instead of being blown off. Observations have therefore been included on the effects of this condition.

With regard to the observations on shock it may be stated that these were undertaken to ascertain whether accumulation of lactic acid might be responsible for the marked depression in the CO_2-combining power of the blood which had been detected by Cannon (9) and his collaborators in severe cases of this condition.

METHODS

Sufficient quantities of arterial blood were delivered into 2 per cent HCl solution and the proteins removed by the addition of $HgCl_2$. After removal of excess Hg, by means of H_2S, the filtrate was brought to small bulk, in faintly acid reaction, by evaporation in a brisk current

of slightly warmed air and then extracted (usually for 48 hours in a Dunbar apparatus) with alcohol-free ether. The ethereal extract was evaporated, the residue oxidized with weak permanganate and the aldehyde resulting from the oxidation of the lactic acid distilled into bisulphite solution and determined colorimetrically. This is not the place to discuss the details or the limitations of this method but it may be said that it has been sufficiently tested, by controls with lithium lactate and by numerous duplicate analyses, to show that it is of sufficient accuracy for the purposes for which it has been used in the present investigation.

RESULTS

We will first of all consider the observations on anoxemia and asphyxia and then those on shock.

Anoxemia. The results are shown in table 1. The anoxemia was induced either by causing the animals to breathe into a closed system of tubes and rubber bags containing soda lime, or into a spirometer containing mixtures of nitrogen and oxygen. Ether was used as an anesthetic, except in experiment K, where urethane was employed. In experiment G some difficulty was experienced in controlling the anesthetic, and just prior to removal of the sample of blood a marked fall in arterial pressure occurred. Partly on this account and partly because no analysis of the air was made, the observation is of little value, although it shows a marked increase in lactic acid. In experiment K the percentage of oxygen fell to 11.9 per cent in 22 minutes, but there was no increase in the lactic acid content of the blood. These are the only experiments of the series in which the results are not perfectly definite.

In experiment L the anoxemia was induced by filling the rebreathing apparatus with a mixture of air and nitrogen to start with, the samples of blood which were removed after anoxemia was established being venous in color, and showing a great increase in lactic acid within 10 minutes after the start, when the oxygen in the inspired air had fallen to about 6 per cent. In experiment M the anoxemia was more slowly induced, a small amount of air being allowed to enter the rebreathing apparatus. In 17 minutes, when the oxygen stood at 8.9 per cent, the percentage of lactic acid in the blood had risen to 0.071, and 12 minutes later, when the oxygen had been reduced to 3.8 per cent, the very high result of 0.123 per cent was obtained. Immediately after the

TABLE 1

Anoxemia

NUMBER AND WEIGHT	TIME	CONDITION	LACTIC ACID IN BLOOD	TIME SINCE ANOXEMIA STARTED	BLOOD PRESSURE	AIR OF SYSTEM CO_2 AND O_2
			per cent	*minutes*	*mm. Hg*	*per cent*
G 4.5 kgm.	10.21	Normal (venous)	0.029		124	
	10.32	Normal*	0.052		50–60	
		Connect with apparatus				
	11.05	Anoxemia	0.088	33	30	
K. 6 kgm.	1.22	Normal	0.057			
	1.25	Connect with apparatus				
	1.30	Anoxemia	0.037	5	110	
	1.43	Anoxemia	0.038	17		CO_2 0.00 O_2 11.9
	1.47					
L. 8.5 kgm.	10.47	Normal	0.049			
	11.15	Connect with apparatus				
	11.25	Anoxemia	0.084	10		
	11.27	Anoxemia	0.098	12		CO_2 0.2 O_2 5.9
		(Air + N. in system at start)				
M. 9.3 kgm.	3.20	Normal	0.038			
	3.21	Connect with apparatus				
	3.30	Anoxemia	0.045	9		
	3.38	Anoxemia	0.071	17		CO_2 0.2 O_2 8.9
	3.49					CO_2 0.1 O_2 3.8
	3.50	Anoxemia	0.123	29		
	4.20	Normal	0.091	(after) 30		
	4.50	Normal	0.065	60		
N. 9 kgm.	10.20	Normal	0.051		122	
	10.40	Normal	0.055			
	11.05	Connect with apparatus				
	11.12	Anoxemia		7	130	CO_2 = 0% O_2 10.3
	11.25	Anoxemia	0.085	20	120	CO_2 0.3 O_2 7.4
	11.45	Anoxemia	0.090	40	100	CO_2 0.3 O_2 4.8
	12.05	Anoxemia				
	12.15	Anoxemia discontinued				
	12.35	Normal	0.094	(after) 20	100	

* Resuscitated after an overdose of ether.

removal of this sample the blood pressure fell rapidly and the respirations ceased, so that the animal was disconnected from the rebreathing apparatus, and artificial respiration, with administration of oxygen by catheter, had to be resorted to to restore it. Samples of blood removed in 30 and 60 minutes after the resuscitation contained 0.091 and 0.065 per cent lactic acid, respectively. The increase in lactic acid was therefore very decided within 17 minutes after the start of anoxemia, and it had become only moderately reduced in 30 minutes after the animal was allowed again to breathe outside air.

Somewhat similar results were obtained in experiment N, in which the anesthetized animal was left undisturbed for one hour, and a second control blood taken before connecting it with the rebreathing apparatus. The two results corresponded closely, corroborating numerous other observations that ether alone does not cause any excess of lactic acid to accumulate in the blood. Twenty minutes after starting anoxemia, when the oxygen stood at 7.4 per cent, the lactic acid had increased to 0.085 per cent, about which it remained for a further similar period, although the anoxemia was gradually becoming more intense, the oxygen falling to 4.8 per cent. The oxygen was maintained at this low level but the sample of blood that was removed after 20 minutes unfortunately came to grief in the analysis. The animal was finally allowed to breathe outside air, and after 20 minutes the lactic acid stood at 0.094 per cent

Here again, anoxemia caused the lactic acid content of the blood to become almost doubled after about 20 minutes, and it remained at this level for at least 20 minutes after the animal was allowed to breathe outside air.

Taking these results as a whole it is clear that considerable reduction in the percentage of oxygen in the inspired air caused the concentration of lactic acid in the arterial blood to become increased by nearly 100 per cent within 15 minutes. Although meanwhile the percentage of oxygen had fallen to considerably less than one-half the normal, there can be no doubt that the acid had begun to make its appearance in excess long before this low level was reached. The exact degree of anoxemia necessary to cause the increase remains however to be determined, the particular question under consideration at present being the time required in conditions of acute anoxemia for a sufficient amount of lactic acid to be discharged from the tissues into the blood to cause an increase that would be expected to have a disturbing influence on the acid-base equilibrium of the organism as a whole. Long

before this, a change in the C_H of the tissues themselves must occur. It is of importance further to note that it takes some considerable time after the anoxemia is terminated for the excess of lactic acid to be got rid of. This may be accomplished partly by oxidation or by conversion into other substances (e. g., glucose) but it is likely that a certain amount of the acid is got rid of by excretion with the urine.

As has already been pointed out, the appearance of excess of lactic acid in the blood in anoxemia does not necessarily mean that it has resulted entirely from the depressed oxidation. Its appearance may rather be of the nature of a protective mechanism in the sense that it

TABLE 2

Asphyxia

NUMBER, WEIGHT OF ANIMAL AND TYPE OF EXPERIMENT	TIME	CONDITION	LACTIC ACID IN BLOOD	DURATION OF PERIOD	BLOOD PRESSURE
			per cent	*minutes*	*mm. Hg*
E.	11.23	Normal			128
8.5 kgm.	11.25½	Asphyxia	0.019	1½	170
Brief periods of acute asphyxia	11.49½	Normal	0.077	(after) 23½	126
	11.59	Asphyxia	0.038	3	110
	12.24	Asphyxia	0.050	25	40
	10.55	Normal	0.0473		110
F.	11.10	Asphyxia			130
5.5 kgm.	11.34	Asphyxia	0.032	24	118
Prolonged asphyxia	11.52	Asphyxia	0.061	42	102
	12.02	Asphyxia	0.101	52	90–102
	12.58	Normal	0.045	(after) 56	40

helps to neutralize the relative excess of alkali resulting from the blowing off of CO_2 which occurs as a consequence of the hyperpnea excited directly by oxygen want. This possibility could be most directly tested by seeing whether lactic acid is produced in excess in cases of forced ventilation of the alveoli. Such experiments are under way and the results will be reported later. The appearance of lactic acid in conditions of carbon monoxide poisoning (2) would seem to show, however, that faulty oxidation of organic radicles is an important cause and the same result in mechanical asphyxia, for reasons that have already been explained, would support this conclusion. The results of two experiments on this condition are shown in table 2.

The asphyxia was induced by clamping the respiratory tube. In experiment E the clamp was completely closed, so as to produce a

condition of acute asphyxia, and there was a great increase in arterial blood pressure followed in about 2 minutes by signs of cardiac failure when the clamp was removed. The sample of blood collected just toward the end of the asphyxial period was very venous in color, but it did not contain any excess of lactic acid; indeed it only contained about one-half the amount usually present (0.019 per cent). The animal was then left undisturbed, and in 23 minutes another sample of blood was found to contain 0.077 per cent lactic acid—a very pronounced increase. In 10 minutes later the percentage had returned to about the normal where it remained for about one-half hour during which period the blood pressure was rapidly falling.

In experiment F the respiratory tube was only partly constricted, causing a moderate degree of asphyxia as judged from the arterial blood pressure (rose from 110 mm. to 130 mm.). A decided increase in lactic acid was observed after 42 minutes. The asphyxia was then made more acute and in 10 minutes the lactic acid had risen to a very high percentage of 0.101. After removal of the clamp the arterial blood pressure gradually fell from 65 mm. Hg. to 40 mm. Hg. and a sample of blood removed 56 minutes later from the vena cava (through a catheter inserted into the femoral vein) contained 0.045 per cent lactic acid. In this experiment, as in the previous one, the increase ln lactic acid was delayed in making its appearance and the normal level was regained within an hour after the asphyxia was terminated.

These results would seem to indicate that anoxemia in the presence of an excess of CO_2 in the blood still causes lactic acid to appear in excess. It is possible however that lactic acid may also be increased in the blood in less acute forms of anoxemia than those investigated in the present research and in conditions of acapnia caused by excessive pulmonary ventilation. Investigation of these possibilities is under way.

SHOCK

In choosing a method to induce shock in laboratory animals it was decided to employ mainly that recommended by Y. Henderson and Haggard (10) and known as "gastric manipulation" especially since Edwards and Wiggers had reported to the Committee on Physiology of the National Research Council, U. S. A., that the animals subjected to such treatment showed, when the ether was discontinued, the characteristic neuro-muscular syndrome, viz., apathy, muscular weakness and paresis with knee jerk intact. The latter observers also found in

TABLE 3

Shock

NUMBER AND WEIGHT OF ANIMAL	MINUTES AFTER START OF DUODENAL IRRITATION	BLOOD PRESSURE	OTHER SYMPTOMS	LACTIC ACID
		mm. Hg		*per cent*
II* 9 kgm.	(Ether)	130	Pulse 192; Temp. 38†	0.107
	60	40	Pulse 120; Temp. 37	
	280	95	Pulse 120	0.070
III* 10 kgm.	(Chloretone)	80	Pulse 128; Temp. 37	0.052
	65‡	46	Temp. 36.5	
	220	60	Pulse 88; Temp. 35.5	0.065
C. 8 kgm.	(Ether)§			0.021
	120			0.019
	160 (after clamp on)	40		0.080
D.	(Ether)			0.038
	100	40**	Respiration deep and rapid	0.042
	140	40††		0.061
	220	below 40	Respiration irregular; Temp. 36.5. Reflexes gone except knee jerks	0.067
	235	Failing rapidly	Moribund when sample taken	0.092
O. 11 kgm.	(Ether)	120		0.032
	30	104	Temp. 37	0.048
	90	80	Temp. 37	0.037
	160	64	Temp. 36	
	210	44	Temp. 37	0.048
	227	Very low	Temp. 37	0.047‡‡
P. 16 kgm.	(Ether)	120	Temp. 37	0.046
	60	104	Respiration irregular and deep; Temp. 37	0.025
	120	86	Respiration slow and shallow	0.036
	180	78	Respiration shallow	0.047
	240	64	Respiration better	0.052
	300	36	Respiration slow and irregular	0.071‡‡
	313	30	Respiration very slow	0.087‡‡
	323	20	Respiration almost stopped	0.090‡‡

* Ether withdrawn 20 minutes after start.

† Temperature in °C.

‡ Massage discontinued.

§ Erlanger's method.

** Massage stopped, but pressure rose.

†† Blood pressure stays low without massage.

‡‡ Blood venous.

60 per cent of the animals experimented on that a fall in blood pressure below 70 mm. Hg. indicated that a progressive circulatory failure was present.

The results are given in table 3. The first two experiments (II and III) were performed conjointly with C. H. Wiggers, who undertook the experimental part of the investigations, the blood after its collection in an acid solution of mercuric chloride being then sent by mail to me for analysis. A period of several days therefore elapsed between the collection and the analysis of the samples.

The results of these two experiments do not show any increase in lactic acid. In one of them (II) there was an unusually high percentage of lactic acid in the sample of blood removed shortly after etherization and after a period of 4½ hours during the earlier part of which the animal had been in profound shock, the percentage was much lower. In the other experiment (III) the "normal" blood contained a moderately high percentage of lactic acid, and after about 4 hours, during a part of which the animal had been in profound shock, a slight increase was observed.[1] In both of the animals the arterial blood pressure was reduced to the shock level of 40 mm. by handling of the stomach. in a relatively short period of time (70 minutes in no. II and 45 minutes in no. III). The animals were then left undisturbed without anesthetic (since they were unconscious) and the blood pressure gradually recovered, the blood samples being removed in from 3 to 4 hours after discontinuance of gastric manipulation. Thereafter the animals were placed in a warm place, but both of them expired during the night. Doctor Wiggers kindly sent several samples of blood in July, 1918, from other shock experiments, but an unfortunate accident to the Lind extraction apparatus, and the impossibility of having this repaired at that time, made the results unreliable.

The investigations have, therefore, been more recently repeated using different methods both for inducing the shock and for the ether extraction of the lactic acid (the Dunbar apparatus). In experiment C it was attempted to bring about shock by the method of partial clamping of the vena cava recommended by Erlanger and Gasser (11).

[1] It should be pointed out in connection with both of these experiments that all of the results are absolutely higher than those of the other experiments reported in this paper, partly because the Lind method of ether extraction was employed in place of that of Dunbar, and partly because no deduction was made for the small traces of bisulphite fixing material that distils over when the reagents alone are used.

The first two results in this experiment are for blood removed before the clamp was applied and the third, for blood removed after the arterial blood pressure had been held at 40 mm. Hg. for 2 hours. A very marked increase in lactic acid occurred, but it cannot be concluded that the condition of shock into which the animal is brought by the clamping is primarily responsible for the increase, because the partial asphyxia of the tissues posterior to the clamp would in itself be sufficient to account for the production of lactic acid. It was decided, therefore, to return to the method in which the shock is induced by manipulation of the duodenum but to continue this for a longer period than that employed in the first experiments.

These experiments are marked D., O. and P. in table 3. Decided increase in lactic acid occurred as a result of shock in D and P, with no definite change in O. In D there was an increase of from 0.04 per cent to 0.06 per cent in about 3 hours during which the duodenum was manipulated practically continuously, and the respirations were quick and deep. Beyond this time, but not before, the manipulations of the duodenum could be discontinued without any rise in blood pressure above the shock level (40 mm. Hg.), and the other symptoms of shock were well marked, such as absence of reflexes, and irregular breathing. The rectal temperature however was only slightly reduced. After a further half-hour in this condition of profound shock the lactic acid increased to 0.067 per cent. Immediately after the removal of this sample of blood, however, the blood pressure, until now fairly constant at about 40 mm. Hg., started to fall, and the respirations to become much slower. Another sample of blood collected 15 minutes later showed a marked increase in lactic acid (0.092 per cent).

In P the results are of a similar character. Until the shock level of blood pressure had been reached the lactic acid did not increase above the normal for this animal. Indeed it showed a temporary decrease, which we have not uncommonly observed to be the case in anesthetized animals, when nothing is done that is likely to increase the accumulation of lactic acid in the blood. It took nearly 5 hours of duodenal irritation to bring the blood pressure permanently to the shock level, and in the three samples of blood removed during the next half-hour a progressive increase in lactic acid up to 0.090 per cent was observed. The results of experiment O do not indicate any decided increase in lactic acid, although the animal (a large one of 11 kgm.) behaved very much like that of P, the only difference being that the blood pressure fell very rapidly and the animal soon became moribund after the shock level had been attained.

We may conclude from these observations that the condition of shock in dogs is not accompanied by an increase in the blood of unoxidized organic acid until the condition has been maintained for some time. The cause for the appearance of the acid is no doubt inadequate circulation in the tissues, leading to partial asphyxia. Indeed, the last samples of blood in experiments D and P were markedly venous in color as they flowed from the artery, and the respirations just prior to their removal had become decidedly inadequate. There is evidence, however, that the lactic acid had increased somewhat before any general condition of asphyxia due to failing respirations occurred.

It is certain that the symptoms of shock are not dependent upon any accumulation of unoxidized organic acid in the circulating fluids, for were this the case, an increased percentage of lactic acid would have been evident in the blood much earlier than was found in these experiments. It is only after a more or less prolonged period of failing circulation that the acid accumulates, and it would appear subsesequently to be removed if the pressure is allowed to rise again, as in experiments II and III. The accumulation in lactic acid which sets in late in shock may be largely responsible for the striking reduction in the alkaline reserve of the blood which has been observed by Cannon and others (9) in cases of severe shock in man, but it is interesting to note that the percentage to which the lactic acid rises under these conditions is much less than that which can be brought about by the injection of alkalies into the blood (7), (8), and is not so high as that caused by conditions of acute anoxemia.

In view of these results it was decided to see whether any increase in lactic acid could be detected in the muscles at earlier stages in shock than those at which the percentage of this substance in the blood could be detected. In this part of the work I was assisted by F. H. Hartman and R. S. Lang. After etherization, the gastrocnemius and semitendinosus muscles were carefully excised without previous disturbance of their blood supply, and very rapidly cooled to near the freezing point in a freezing mixture. After weighing (being still kept cool), they were chopped up in an ice-cold mortar and ground along with quartz sand in ice-cold alcohol and strained through gauze. The extractions were repeated until the alcoholic extracts gave no decided test for lactic acid by thiophene. Since it was important to get rid of all traces of alcohol before the lactic acid could be determined by oxidation with permanganate the alcoholic extracts were then evaporated to dryness by moderate heat, and the residue extracted with

weak 0.2 per cent HCl and mixed with $HgCl_2$ solution. This caused a satisfactory precipitation of proteins, etc., and after filtration the excess of mercury was removed by H_2S. Thereafter the lactic acid was estimated by the same method as for blood.[2]

The percentages of lactic acid found present in normal muscles by the above method in the different experiments were as follows:

Gastrocnemius: (I) 0.105; (III) 0.074; (IV) 0.150 (high result probably due to rise in temperature before alcohol added).

Semitendinosus: (I) 0.080; (II) 0.066; (III) 0.053; (IV) 0.044.

The percentages found in the corresponding muscles of the opposite leg after profound shock had been produced were as follows:

Gastrocnemius: (II) 0.076; (V) 0.099; (VI) 0.045; (VII) 0.048;

Semitendinosus: (I) 0.158; (II) 0.073; (IV) 0.087; (V) 0.181; (VI) 0.080; (VII) 0.100.

It is evident that definite conclusions are not permissible from among results that are so inconstant in character. As is well known from the work of F. G. Hopkins and Fletcher, accumulation of lactic acid occurs so rapidly in muscle after the circulation has ceased that it is very difficult to secure constant values even when the conditions are most rigorously controlled. In preliminary experiments we have found it easy to demonstrate this rapid accumulation of lactic acid in excised mammalian muscle, but we had hoped to be able by strictly following the same procedure in all of the "shock" experiments to secure results of tolerable constancy.

CONCLUSIONS

The percentage of lactic acid in the blood has been determined in conditions of *anoxemia* with the following results:

1. In acute anoxemia a marked increase occurred within 10 minutes of the start of the condition.

2. In more gradual anoxemia a similar increase occurred within 17 to 20 minutes, no increase being evident in one experiment of this nature in 9 minutes.

3. After termination of the anoxemia the return to the normal percentage was relatively slow, being evident in one experiment in 1 hour but not so in another in 20 minutes.

It is pointed out that these results do not support the view that the appearance of an excess of lactic acid bears any relationship to the

[2] This method was found to be more satisfactory than that in which the watery extract is treated with charcoal or with well-washed lead carbonate.

stimulation of the respiratory center. It is suggested that the excess of lactic acid in anoxemia may perform the function of assisting in the neutralization of the relatively increased base which results from the blowing off of CO_2 from the blood, this being dependent upon stimulation of the respiratory center by the oxygen deficiency. No evidence has been secured to show whether lactic acid can be produced for this purpose when there is no deficiency of oxygen in the tissues but the fact that it appears in *mechanical asphyxia*, in which CO_2 is also present in excess, is confirmed. After a short period of complete obstruction of the trachea an increase in lactic acid was observed in 23 minutes and after a longer period of partial obstruction in 42 minutes.

Observations were also made on the percentage of lactic acid in the blood at various stages in *experimental shock* caused by manipulation of the duodenum. It was found that no increase occurred until the condition was so far advanced that the arterial blood pressure did not rise above 40 mm. Hg. on discontinuance of the manipulation and the respiration had become slow and irregular. Several hours of manipulation were required to bring about this state and since it is known that a condition of shock that is ultimately fatal becomes established at a much earlier stage it is concluded that the appearance of lactic acid in the blood has no casual relationship to the establishment of the condition. The lactic acid appears in excess in the blood in shock only after the respiratory and circulatory functions have become so greatly depressed that a condition of anoxemia exists.

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A COMPARISON OF THE ELECTRICAL CONDUCTANCE OF ELECTROLYTES AND THEIR TOXICITIES TO FISH

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Almost from the beginning of the knowledge of certain of the physical and chemical properties of inorganic substances much interest has been centered in attempting to determine the causes of their physiological actions. Workers have not agreed as to the exact cause of the toxicities of the elements or the mechanism of their activities. Blake (1), (2) held that the toxicities of isomerous groups were associated with their atomic weights. Botkin (3) claims that their toxicity is related to their position in the periodic system. Mathews (4) has suggested solution tension as a function of physiological activity.

In connection with the study of the effect of temperature and concentration on the toxicity of salts to fishes (5) work was undertaken to determine if the variation in their physiological activities is in any way parallel to their electrical conductance. A number of experiments was performed to elucidate this point.

Methods. The method for carrying on the experiments at a constant temperature has already been described (5). The blunt-nosed minnow (*Pimephales notatus* Raf.) of about 1.5 to 3.5 grams was used in all observations. The relative electrical conductance of the solutions was determined with a Washburn conductivity cell modified especially for this work, and a Wheatstone bridge. A telephone receiver with a fundamental vibration of 1000 per second was employed instead of a galvanometer. The alternating current was generated by a small Leeds and Northrup high frequency generator driven by two storage batteries and regulated to produce 500 cycles per second.

Experimental data. A number of experiments was run with solutions of each of the chlorides of sodium, calcium, barium and magnesium with concentrations between about 0.025 N to about 0.333 N. at 12.8°, 17.8°, 22.8°, 27.8° and 32.8°C. Table 1 gives a summary of the results. The velocity of fatality (the survival time over 100) is the average of

that of two or more fish killed in each of the different concentrations at the given temperatures. The relative electrical conductance of each solution at the time and temperature of the experiment is given instead of the actual electrical conductance.

TABLE I

A comparison of the velocity of fatality of the blunt-nosed minnow (Pimephales notatus Raf.) when killed in NaCl, $CaCl_2$, $BaCl_2$ and $MgCl_2$ and the relative conductance of the solutions used

SUBSTANCE	NORMAL	12.8°C.		17.8°C.		22.8°C.		27.8°C.		32.8°C.	
		Velocity of fatality	Relative conductance	Velocity of fatality	Relative conductance	Velocity of fatality	Relative conductance	Velocity of fatality	Relative conductance	Velocity of fatality	Relative conductance
NaCl	0.025	0.005	0.91	0.010	1.00	0.015	1.15	0.140	1.20	1.870	1.37
$CaCl_2$	0.025	0.006	0.99	0.014	0.98	0.025	1.14	0.100	1.19	1.670	1.37
$BaCl_2$	0.025	0.190	0.82	0.740	0.95	0.240	1.09	1.875	1.18	6.345	1.30
$MgCl_2$	0.025	0.065	0.85	0.005	0.98	0.020	1.05	0.045	1.17	5.710	1.29
NaCl	0.050	0.165	1.66	0.040	1.95	0.016	2.18	0.140	2.42	1.525	2.62
$CaCl_2$	0.050	0.006	1.64	0.015	1.84	0.040		0.145	2.29	1.225	2.51
$BaCl_2$	0.050	0.545	1.61	1.485	1.81	1.705	2.18	2.560	2.21	5.545	2.47
$MgCl_2$	0.050	0.020	1.60	0.003	1.82	0.030	2.04	0.120	2.32	1.975	2.47
NaCl	0.100	0.100	3.33	0.013	3.75	0.140	4.22	0.705	4.53	1.258	5.03
$CaCl_2$	0.100	0.015	3.00	0.020	3.53	0.048	3.83	0.245	4.29	1.300	4.60
$BaCl_2$	0.100	1.850	3.01			3.035	3.82	14.370	4.22		
$MgCl_2$	0.100	0.012	3.06	0.013	3.44	0.620	3.84	0.515	4.22	1.815	
NaCl	0.227	0.375	7.12	0.380	7.95	1.695	8.95	1.945	9.76		
$CaCl_2$	0.227	0.185	6.51	0.485	7.34	1.370	7.85	1.850	8.80	2.330	
$BaCl_2$	0.227	3.005	6.37	5.290	7.23	7.690	7.99	15.390	8.81		
$MgCl_2$	0.227	1.220	6.36	0.795	7.33	1.055	8.00	1.675	8.74		
NaCl	0.250	0.855	7.72	0.645	8.72	1.370	9.71	2.720	10.66		
$CaCl_2$	0.250	0.860	7.05	0.670	8.01	1.310	8.92	2.720	9.83		
$BaCl_2$	0.250	2.775	6.98	4.905	7.88	9.090	8.65	18.180	9.62		
$MgCl_2$	0.250	0.470	6.90	1.080	7.85	1.370	8.00	4.375	9.48		
NaCl	0.275	0.770	8.48	1.045	9.51	2.810	10.66	2.940	11.60		
$CaCl_2$	0.275	1.225	7.38	1.665	8.53	1.855	9.52	2.95	11.60		
$BaCl_2$	0.275	3.030	7.64	5.325	8.51	10.555	9.38	17.785			
$MgCl_2$	0.275	0.870	7.49	1.665	8.22	2.145	9.36	4.300	10.27		
NaCl	0.302	0.950	9.22	1.940	10.37	4.350	11.51	6.350	12.90		
$CaCl_2$	0.302	1.335	8.51	1.765	9.48	2.730	10.60	6.350	12.93		
$BaCl_2$	0.302	3.850	8.30	5.880	9.34	10.000	10.36	22.220	12.37		
$MgCl_2$	0.302	1.640	8.12	1.645	9.29	2.860	10.30	4.025	11.30		
NaCl	0.333	1.275	10.37	1.770	11.37	4.720	12.63	7.945	13.94		
$CaCl_2$	0.333	1.440	9.22	2.815	10.50	3.490		7.945	13.94		
$BaCl_2$	0.333	4.675	9.07	11.900		12.135	11.27	28.590			
$MgCl_2$	0.333	1.215	8.94	2.195	10.12	2.685	11.30	6.170	12.12		

Discussion. When the relative toxicities of the chlorides of sodium, magnesium, calcium and barium are approximated at 17.8°C. by taking the theoretical velocity of fatality curve as a criterion for the measurement of relative toxicity (6), it is found that they arrange themselves in the order named, with the least toxic first and the most toxic last. This can be only an approximation, since there were only a few experiments made in the straight line limits of the velocity of fatality curves which seem to approximate 0.23 N. to 0.28 N. at least for the first three chlorides named. But when the velocities of fatality of each of the concentrations at the different temperatures tested are averaged for each salt, and the average taken as a criterion for the relative toxicity, the arrangement of the salts in order of their relative toxicities is somewhat different. They arrange themselves as follows: Magnesium chloride, calcium chloride, sodium chloride and barium chloride, with the least toxic first and the most toxic last. The position of the sodium chloride is due to the high velocities of fatality of the fish in this substance at 22.8° and 27.8°C. These two sets of experiments seem to be erratic as compared with other temperatures at which the sodium chloride was tested, and also when the theoretical velocity of fatality curve criterion is applied to the data at these high temperatures. However, neither of these orders given for the relative toxicities of the salts corresponds to the order of electrical conductance of the solutions of equivalent normalities at a given temperature (see table 1).

When the data of table 1 are compared it is found that there is no direct agreement in the relative toxicities of the electrolytes and the electrical conductance of different concentrations at any one temperature. There is, however, an indirect relation between the two in so far as the curves representing the physiological activities and the electrical conductance are constant. Compare the survival time and velocity of fatality curves of electrolytes to goldfish (6) and the electrical conductance, table 1. It might be expected that the variation in the specific forms of the velocity of fatality curves of the fish when killed in solutions of different concentrations of electrolytes would bear some relation to the curves representing the electrical conductance of the solutions. The data at hand do not warrant such a conclusion.

SUMMARY

These experiments seem to indicate that there is no direct relation between the relative toxicities of the electrolytes and their relative electrical conductance, when either the theoretical velocity of fatality curve

or the actual velocity of fatality of the fish is taken as a criterion. There is no direct agreement between the survival time or the velocity of fatality curves of the fish and the electrical conductance of the electrolytes tested.

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LIGHT-SPOT ADAPTATION

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I. THE GENERAL PHENOMENA AND OBSERVATION

In some earlier work[1] I found that a patch of light of a certain brightness, seen peripherally against an otherwise dark field, would disappear in a few seconds, if fixation were accurately maintained. Without attempting to determine the effects of area, brightness, visual angle and adaptation, I investigated at that time the peculiar after-effects of the physical extinction of the light-spot, subsequent to its apparent disappearance. The apparatus for this investigation was very simple: a dim light in a box, with a pin hole covered by white paper, served as a fixation mark; and a milk-glass window in a larger box, with a brighter light, furnished the light-spot for observation. The light behind the milk-glass window could be extinguished by means of a snap switch, and the window could be covered by various color screens. Any desired angle between fixation point and spot was secured by placing the two boxes properly on a table at definite distance from each other and from the observer's eye.

I found that the extinction of the light, after the spot had disappeared (that is, after the entire visual field except the fixation point had become uniformly dark) was always visible: sometimes as a momentary reappearance of the light, sometimes as the appearance of a darker spot, and sometimes as a coronal effect surrounding the area where the spot had disappeared. When colored spots were used, the after-appearance in the area of the spot, or the corona, was sometimes of the same color as the primary spot, sometimes complementary, and sometimes neither.

At this point the work was dropped, on account of press of other matter. Brief mention was made of the phenomena (Dunlap, op. cit.

[1] Dunlap, K. Die Wirkung gleichzeitiger Reizung von Zentralen und Exzentrischer Netztrautstellen. 1912, Arch. f. Psychol., xxiv, 299-304.

pp. 302–303) and I have been employing it in an exercise in my laboratory course since that time. In the summer of 1920, through the courtesy of Dr. E. P. Hyde, Director of the Nela Research Laboratory, an opportunity was given to resume the investigation of this most interesting phenomenon. The investigation, as will be seen from the following report, is still in the exploratory stage, but the observations thus far seem of enough interest to warrant their presentation.

The apparatus employed is similar to that of the first investigation. A light-tight metal box, 11 inches long, 8 inches high and 8 inches wide, encloses a receptacle in which bulbs of any desired wattage may be inserted. In the center of one end of the box is a square window, $3\frac{1}{2}$ x $3\frac{1}{2}$ inches, provided with guides and springs, so that plates of glass and metal diaphragms may be slipped over the window. Between the window and the lamp receptacle, an 8 inch square of ground glass is inserted as a diffusing screen. Cardboard diaphragms, or absorbing screens, are used in contact with the ground glass to reduce the light.

The lamp box was supported on a table at the approximate height of the seated reactor's eyes. A gray cardboard screen, erected just in front of the box window, and having a 3-inch square aperture centered on the window, hid the apparatus. In the work here reported, a square of flashed white glass was used in the window, a 10-watt mazda bulb in the receptacle, and diaphragms; which gave a brightness of approximately 3 apparent foot candles on the white glass in the reactor's direction. The glass was covered by one of a set of diaphragms of apertures as specified below, thus regulating the area of the light-spot.

As a fixation mark, the filament of a 2 c.p. miniature lamp was used. By means of rheostats, the current through this lamp was fixed at such a value that the central part of the filament glowed distinctly, but not brightly; it was barely luminous in daylight, but very clear in the darkened room. The relative position of miniature lamp and lamp-box could be so varied as to give any desired angle of vision between fixation point and light spot, within the limits of 15 and 45 degrees.

A forehead and chin rest was fastened rigidly to a table in front of the light spot, so that the reactor's eyes were approximately a meter and a half from the light spot. The light spot was kept in fixed position, and the fixation point moved to obtain the desired angles. This method, as well as the converse method, of keeping the fixation point in constant position and varying the position of the light spot, has, perhaps, certain theoretical disadvantages, but the method employed was satisfactory, and sufficiently accurate. In the first set of observa-

tions, where the effects of angular variation were investigated, the head was turned to face the fixation point. In the other work, the head was kept in fixed position, facing the light spot directly, and the eyes turned to the fixation point. For angles no greater than 30°, either method gave practically the same ease of observation. Discrepancies in measurement, due to turning the head, are small enough to be negligible in the present observations.

About two weeks time was consumed in unsystematic observation. It was quickly certified that steady fixation was the essential point in the phenomenon and that adaptation, area and brightness were very influential. A spot of given area and brightness, at a fixed angle, which would disappear in from two to three seconds when the observation was made with as near daylight adaptation as possible (e.g., the reactor coming in to the observation room from a brightly daylit room) required a much longer period for disappearance after even a few minutes of darkness adaptation. The effects of area and brightness may be summarized in the statement that the smaller and dimmer the light, the more quickly it would disappear. It was not evident from the first observations that the angle of vision had a definite influence, and therefore a brief systematic set of observations on this point was made by the author, as soon as sufficient practice in fixation had been acquired.

II. THE EFFECT OF ANGLE

For these observations a diaphragm of 1 cm. diameter circular aperture (a light-spot of 1 cm. diameter therefore) was employed; and the horizontal angular distances of 15°, 30° and 45° from the fixation point were chosen. In each set, ten observations with each eye and ten with both eyes were made with each angle, with the spot at the right of the fixation mark; and the same number with the spot at the left. This total of 180 observations was all that could be made without serious fatigue, in a period of from two to three hours, and but one such period could be efficiently utilized in one day.

With the spot at a given angle on the right of the fixation mark, the left eye was covered and an observation made with the right eye; then the right eye was covered and an observation made with the left, and so on alternately until ten observations had been made with each eye. Then ten observations were made with both eyes together. Next, the fixation mark was changed so that the spot was on the left, at the same angle as before, and the procedure repeated. The two other angles

were next employed in the same way. Three sets were carried out, the order of angles being 30°, 15°, 45° in the first; 15°, 45°, 30° in the second, and 45°, 30°, 15° in the third.

Times were taken with a stop-watch, a faint light from a miniature lamp with reduced current being employed momentarily in reading the watch and writing the numbers. This undoubtedly interfered with the adaptation, to a slight extent, but the interference was fairly constant and not consequential. Work was commenced in each set after thirty minutes darkness adaptation. No measured interval was used between observations, but the eyes rested a few seconds each time before making a new observation.

In case of a "balk" or failure to finish an observation, in the monocular series, the next observation was made with the other eye as if the first observation had been completed. Balks were fairly frequent and were due to two causes: *a*, uncontrollable movement of the eyes, before the observation was finished; *b*, eye strain, which at times became too unpleasant to allow the observation to be completed, although no discernible movement had occurred.

With the area, intensity and adaptation employed, the spot might disappear without complete darkening of the field. A haze or blur of diffused light was discernible, covering a considerable part of the visual field around the spot, and this haze of light remained after the brighter spot had disappeared. Occasionally the spot left a corona of light when it disappeared, but the observation in that case was not completed until the corona had disappeared also. It was possible to make the residual haze disappear, but this required such prolonged fixation that the eye strain and frequent balks prevented the carrying of many observations to this point.

The haze above described may perhaps be due to light diffused by cornea and lens. At any rate, a very small degree of light adaptation is sufficient to prevent the appearance of the haze, and hence make the observation much more sharp.

Two methods of fixation were tried. The simplest technically is to obtain fixation before switching on the light-spot, starting the watch as the spot appears. The appearance of the spot is, however, apt to occasion a slight eye movement and to require fixation anew. Hence in these series another method was employed, although later, after more practice, it was possible to use the first named method successfully.

In the method employed in these series, the spot was kept constantly illuminated, and the eyes, which had been closed for a few seconds

previous to the observation, were directed to the right or left of the fixation mark, then moved across it and then back to fixation, the watch being started after the eyes came to fixation. This oscillatory method gave better fixation than did the attempt to fixate directly. When the light-spot disappeared, the watch was stopped and the reading taken.

These observations were, of course, rough and theoretically subject to disturbance, through the same person being both reactor and recorder. (No other trained observer was available, and the observation of persons not carefully trained for the task are of little value.) Measurements were taken to the nearest second.

The results of the observations are given in the following table, in which each value is the average of ten measurements.

TABLE 1

First day

	ANGLE	RIGHT EYE	LEFT EYE	BOTH
		seconds	*seconds*	*seconds*
I	30° Rt.	*5.8*	6.9	5.3
II	30° Lf.	6.3	*5.8*	5.2
III	15° Rt.	*6.0*	7.4	4.5
IV	15° Lf.	5.0	*5.9*	4.2
V	45° Rt.	*5.9*	5.8	5.2
VI	45° Lf.	5.7	*5.3*	4.5
		Second day		
I	15° Rt.	*5.6*	5.1	5.1
II	15° Lf.	5.8	*5.4*	3.6
III	45° Rt.	*4.1*	4.3	4.7
IV	45° Lf.	5.5	*4.5*	4.8
V	30° Rt.	*3.4*	5.5	5.2
VI	30° Lf.	5.2	*4.0*	5.3
		Third day		
I	45° Rt.	*5.0*	5.7	5.0
II	45° Lf.	6.5	*6.1*	5.7
III	30° Rt.	*5.1*	5.6	5.8
IV	30° Lf.	6.7	*5.1*	5.7
V	15° Rt.	*6.1*	6.2	7.5
VI	15° Lf.	7.1	*6.6*	6.1

The values for measurements for the nasal position of the light-spot angle on the retinae are in italics.

Table 1. The results show no definite effect of varying the angle of vision. Averaging the results for the eyes separately gives value of 5.8, 5.4 and 5.1 seconds respectively for 15°, 30° and 45° angles for the right eye; and 5.3, 5.6 and 5.6 seconds for the same angles with the left eye, and 5.1, 5.4 and 4.9 for binocular vision.

It is by no means to be concluded that the angle is not important, but merely that the differences, if any, corresponding to the angular differences, are too small to appear in observations of the degree of precision here used.

The angular positions of the light-spot in these observations were horizontal only. I have not yet considered the possible effects of vertical variations. The horizontal variations alone are the ones important for the observations next proposed. The systematic exploration of the entire retinal field is a large problem which must be taken up by itself.

The difference between the nasal and temporal fields is more important. In most of the series the spot disappeared more quickly, on the average, when falling in the nasal retinal field (right, right eye; left, left eye) than on the temporal retinal field (left, right eye; right, left eye). The average time for the three angular positions on the nasal retina are: 5.3, 4.8 and 5.0; and for the same angular positions on the temporal side; 5.8, 6.0 and 5.5. The general average for the nasal side is 5.0; for the temporal side, 5.8. This may be due to retinal conditions but is more probably due to the greater tendency to eye movements in the latter case. It was noticed throughout that eye movements were avoided with more difficulty, and eye strain was greater, when the spot fell on the nasal side of the fovea than when it fell on the temporal side.

The time of binocular vision tends to be a trifle shorter (5.1 on the average as compared with 5.5) than when either eye is used alone, which again is perhaps due to the greater ease of fixation when both eyes are used.

III. BINOCULAR PHENOMENA

My earlier observations had been chiefly on the phenomena produced by extinguishing the light-spot (physically) after it had disappeared from vision. I now made attempts to find what happened when the spot was extinguished for a brief moment only, after visual disappearance. For this purpose fixation was maintained until the spot disappeared, and then the light in the light box was snapped off.

and immediately on again, by manipulation of the pendant switch. In these cases I found that the spot was immediately visible when the light was again snapped on. The snapping of the switch did not, however, seem a satisfactory method of procedure, and it seemed possible that eye movement, or eye innervation, occurred simultaneously with the snapping of the switch.

For further work a shutter was arranged in front of the eyes. This shutter was so made that it could be operated by a finger movement, and by its operation shielded one eye from the spot while exposing the other. In the middle position of the shutter both eyes were exposed; so that, starting from the extreme position in which (let us say) only the right eye was exposed, moving the shutter to the other extreme first exposed the left eye, and then shielded the right eye. Moving the shutter back to the first position reversed the process.

The parts of the shutter which came in front of the eyes were so made as to shield the eyes from the spot, but not from the fixation point. In any position of the shutter, therefore, both eyes saw the fixation point, and steady fixation with accurate convergence was thereby facilitated. By the use of this shutter, working with darkness adaptation, and with size and brightness of spot as in II, several interesting phenomena were discovered. In the account which follows, the eye primarily exposed to the spot is called the S-eye, and the one shielded during the primary exposure the D-eye.

1. If, as soon as the spot has disappeared, the stimulation is shifted to the D-eye, (cut off, therefore, from the S-eye) and then shifted back to the S-eye, the spot is visible to the D-eye during all, or the first part of, its exposure, but is still invisible to the S-eye upon its reëxposure. In other words: the inhibition of the S-eye (or of the stimulated area in the S-eye) persists during the exposure of the D-eye, and the reëxposure of the S-eye. There seem to be no time-limits to this persistence of inhibition, except in so far as eye-movements are finally brought in. Prolongation of the second phase of the observation (the exposure of the D-eye) tends to cause disappearance of the spot for that eye also.

2. If, before the spot has disappeared for the S-eye, the stimulation is shifted to the D-eye for a brief time, and then back to the S-eye, it is found in many cases that the S-eye has become inhibited: that is, the spot, still visible when the stimulation was removed for the S-eye, is invisible upon the stimulation being restored to the S-eye.

3. If prolonged exposure of the S-eye is given, beyond the time of disappearance of the spot, and the stimulus is then shifted to the

D-eye, it is found in many cases that the D-eye (or the area of the spot image in the D-eye) is also completely inhibited. The shutter may now be moved back and forth, exposing the two eyes alternately, and the spot will be completely invisible until eye movement occurs.

The primary stimulation required for this phenomenon is lengthy, and I have not succeeded in obtaining it without a few slight eye-movements intervening, which of course still further lengthens the time. Thirty seconds to a minute is usually sufficient.

4. If the D-eye is protected by a separate cover, so that the removal of the stimulus from the S-eye does not expose the D-eye, it is possible to obtain an inhibition which will last over a brief period of removal of the stimulus. That is, moving the shutter so as to cover and then re-expose the S-eye, may find that eye still inhibited on reëxposure. This is the phenomenon I had failed to find, while I depended on the snapping of the light off and on for removal of stimulus and reëxposure. This phenomenon is very much more difficult to obtain than the result described under 1, and the inhibition seems to be destroyed shortly after reëxposure. The difficulty of carrying the inhibition over the dark interval in this case contrasts strongly with the ease with which the phenomenon described in 1 may be obtained.

5. If a prism of small angle be so placed before the D-eye that the D-eye sees the spot through the prism, but sees the fixation point without interference by the prism, and so that the prism does not intervene between the S-eye and either the spot or the fixation point; the phenomena described under 1, 2 and 3, above, *can not be obtained.* In this case, the images of the spot on the two retinae are on non-corresponding points. Obviously, the inhibition obtained in one eye by stimulation of an area in the other eye is principally for the corresponding points only. However, there were some cases in which stimulation of an area in the D-eye very near that corresponding to the stimulated area in the S-eye seemed to prevent the disappearance of the inhibition in the S-eye, after stimulation was removed therefrom.

The persistence of the inhibition in this case may have been merely a case of the phenomenon described under 4. Nevertheless, it would not be possible to say from the present results that the inhibitory effect of stimulation is strictly confined to the stimulated area, and the corresponding area in the other eye.

After making observations with the spot-image displaced to various non-corresponding points in the D-eye, a more striking observation was made as follows: Two light-spots, each approximately 1 cm. in

diameter, and 5 cm. apart on the horizontal line, were employed. These were obtained by placing over the window in the light-box a metal slide with two apertures. A narrow vertical screen was so placed between the observer's eyes and the light-box that the S-eye, when exposed by the shutter, saw only one spot, but the D-eye saw both. The fixation point was visible to both eyes as before.

After proper exposure of the S-eye, the D-eye, when exposed, saw one spot only; the spot to which the S-eye had been exposed being invisible, but the other spot being as clearly visible as on any first exposure. This observation is extremely definite and indicates unmistakably that the inhibition of the unexposed eye is chiefly confined to the area corresponding to that stimulated in the exposed eye.

IV. EFFECTS OF AREA AND BRIGHTNESS

Observations were made with spots of 2 cm. and 3 cm. diameter, using the same brightness as above. The larger spots required distinctly longer fixation for disappearance than did the 1 cm. spot. Although observations with the larger spots were continued several days, no satisfactory time measurements were obtained, because even with the 2 cm. spot the required fixation time was so long that slight eye-movements occurred during its course, still further lengthening it.

Increased brightness of the spot also lengthened the disappearance time, and lowered brightness shortened it slightly. With brightness much above that used in the first observation, the eye strain was so increased as to make observations very difficult. The observations on area and brightness effects must be considered very unsatisfactory, and there was no chance of improving them. The observations are fatiguing and the effects on the eye mechanism were such that prolonged observation finally became impossible. At the end of three weeks work, a half-hour's work on any day produced disagreeable strain, and the more important practical effect of rendering fixation less secure. The lowered efficiency in observation, as well as the consideration of the health of the eyes, indicated the suspension of the work, for the time being at least.

One minor observation is not without interest. It is well known that an observer using one eye only is commonly unable to tell which eye he is using, if the experiment is so conducted that no accessory stimulations give him the clue. This fact may be clearly demonstrated with a shutter such as is above described, by which an assistant can

shift the stimulation from one of the observer's eyes to the other at will, if the observation is conducted in a room sufficiently dark, and with an object (such as the light-spot) not too brightly illuminated, so that the shutter itself is not seen. It was found, however, that in the prolonged observations, it was very easy to identify the exposed eye by the strain localized therein, or in its vicinity. It is impossible to localize the strain definitely in the eyeball. It may well be in the external ocular muscles, although some of it seems to be intra-ocular.

V. GENERAL CONCLUSIONS

While definite conclusions can not be drawn from a few observations obtained with such difficulty, there are certain important questions raised by the data which ought to be given full attention.

Whatever may be the case in ordinary light adaptation and darkness adaptation, the inhibition obtained in these observations is evidently not a purely retinal affair. The fact that the vision of one eye can be inhibited by stimulation of the other eye, distinctly indicates that some part of the central mechanism, connected with both eyes, is involved in the production of the effect. For this reason I have used the term *inhibition* rather than *adaptation*. Although the observations necessarily raise the question whether the well-known phenomena of darkness adaptation may not be in part a central phenomenon, and not exclusively retinal, as is too easily assumed, the two phenomena should be considered separately until it is possible to relate them positively. For the present, the phenomenon of the disappearance of a stimulus in the manner described above must be given a separate name.

The most interesting point concerns the relation of the phenomena to eye-movement, and brings into consideration at once the well-known anesthesia of the visual mechanism during "voluntary" eye-movements. It might at first be supposed that the disappearance of the spot is due to an eye-movement: but this is conclusively disproved by the observation under 5 above, where one spot disappeared and the other did not. Movement tends, in every case, to restore sensitivity (or to be followed by its restoration); and even a very slight movement may temporarily restore it. I am not certain but that *innervation* without movement will do the same. The fact that, when fixation is maintained for a number of seconds after the disappearance of the spot, the spot *stays out*, is in itself conclusive. If the impression of steady fixation were illusory, and the eye actually executed a series of

movements, there would be, if the inhibition consisted merely of the ordinary anesthesia during movement, a succession of disappearances and reappearances, and not continuous absence.

On the other hand, the restorative effect of eye-movement may explain the ordinary anesthesia during movement. We may well assume that the stimulatory process caused by light falling on the retina "runs down," as the physical stimulation is continued with eye at rest, and that the restoring or re-sensitizing of the apparatus occurs at the moment of movement, and that during this brief period of restoration, visual response (the flow of nerve current from the retinal receptors) is interrupted. Naturally, therefore, this restoration should occur most efficiently during eye-movement, since at that time the interruption is not only not an interference with vision, but is a positive assistance, because it prevents the blurring of the field which would otherwise occur.

It should be noted that in addition to central inhibition, a central effect of invisible light is demonstrated by these observations: which is of importance in present problems of illuminating engineering.

I believe that an interesting and important field of research is opened up by these observations, and that the results thereof will help in the understanding of various visual phenomena which are now obscure. The observations required for further experimental work can not be casually made. Long training in oblique vision, as well as the best obtainable psychological technique, are required to make the observations reliable.

STUDIES ON THE VISCERAL SENSORY NERVOUS SYSTEM

VI. Lung Automatism and Lung Reflexes in Cryptobranchus, with Further Notes on the Physiology of the Lung of Necturus

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It seemed to us desirable to determine whether the motor phenomena of the lungs of the *air*-breathing salamander, cryptobranchus, involved physiological mechanisms similar to or identical with those found in the other more *gill*-breathing salamanders (necturus and axolotl). We take the liberty to append data on the physiology of the lung of the necturus which we have collected since the publication of our first observations on this amphibian group (1).

METHODS

Cryptobranchus. Our experimental results were obtained from three quite active specimens. On the basis of our previous experience with salamanders we varied our operative procedures in order to cover the chief points of interest as determined in the other forms.

In one animal the spinal cord was pithed below the medulla. The animal was laid on its back and lungs exposed by ventral incision. A cannula was tied into the tip of one lung. Intercommunication between the lungs was prevented by pressure of a pad of cotton held tightly over the tracheal sac by a rubber band. This procedure also prevented communication of the lung with the pharynx through the glottis. A water manometer was used to record the intrapulmonic pressure of the lung thus isolated except for its blood supply and nervous connections with the medullary center. This preparation was used exclusively for a study of the effects of destruction of the brain (specifically the medulla) on the lung as well as for effects of stimulation of the peripheral end of the vagus on the lung.

Pithing of the spinal cord below the medulla precluded the possibility of obtaining any lung reflexes from stimulation of any cutaneous

or visceral nerves below the point of spinal transection. We therefore immobilized a second specimen by the subcutaneous injection of a suitable dose of curare (0.5 cc. of 1 per cent sol.). After motor paralysis was complete we laid the animal on its back and isolated the lung for manometric records in a manner similar to the first animal. Numerous organs and efferent nerves were stimulated to induce, if possible, reflex contractions of the lung before destroying the medulla and again noting the effect of this procedure on the musculature of the lung.

In another animal an attempt was made to render the animal quiescent without destruction of the spinal cord below the medulla or the use of curare by the application about the fore limbs and hind limbs of tightly constricting rubber bands; for this method had served us well in a previous study on other amphibia (frog, necturus). The animal was rendered quiescent but all attempts at inducing lung contractions reflexly over a period of three hours were futile. We are not certain of the cause of our failure. Since subsequent destruction of the medulla had the usual effect on the lung we are inclined to believe that our failure to induce lung reflexes was due not to a poor physiological condition of the animal but to an exceedingly powerful control of the lung motor center on the lung brought about and maintained by the constant stream of sensory impulses from the cutaneous areas subjected to stimulation by the tightly applied rubber bands.

Necturus. As regards the additional results obtained from several necturi, the methods were similar to those previously used, with only slight modifications. Since we desired to investigate the relation of the higher centers to the lung motor center in the medulla it was, of course, necessary after pithing the animal to place it on its ventral surface and expose the lung by incisions through the back in order to be able to expose and stimulate the cerebral hemispheres, optic lobes and medulla with a faradic current using the unipolar method of stimulation. We employed the technic previously described to prevent the lungs from communicating with one another through the tracheal sac and with the pharynx through the glottis. Since we previously found that certain drugs which have been assumed to be direct stimulants of smooth muscle either had no effect on the musculature of this lung when injected into the circulation or directly applied to the lung (pituitrin) or caused contractions only after previous nicotinization (histamine) (1), it seemed desirable to determine the effect of barium chloride (1 per cent). We concluded the work with the irrigation of the lung with Ringer's solution heated to various temperatures.

RESULTS

Cryptobranchus

The central inhibitory control of the lungs through the vagi. 1. Pithing the medulla or section of the vagi nerves induces immediately a persistent hypertonus or tetanus of the lungs (fig. 1), apparently identical with that seen in the other salamanders (1) and in the frog (2). These were acute experiments, lasting from 2 to 6 hours. The lung tetanus persists during the period of observation, and it is most extreme at the apical third of the lung. Superimposed on the lung tetanus there is usually a slow tonus rhythm (fig. 1). This tonus rhythm is so slow and feeble that we were unable to determine whether it partakes of the nature of the rhythmical segmentation movements or the peristalsis of the gut.

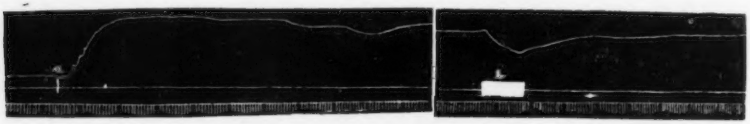

Fig. 1. Water manometer records of the intrapulmonic pressure of cryptobranchus. Spinal cord sectioned just below medulla and pithed. Animal on back. Cannula in tip of right lung. Glottis closed off with hemostat. Pressure over tracheal sac to prevent intercommunication between lungs. *a*, Pithed brain; *b*, electrical stimulation of peripheral end of right vagus. Time, 5 seconds.[1]

Showing escape of lung from tonic inhibitory control on destruction of the medulla and the inhibition of the lung resulting from electrical stimulation of the peripheral end of the vagus nerve.

2. Stimulation of the peripheral end of the cut vagus causes a temporary inhibition of the lung tetanus induced by the destruction of the brain (fig. 1, *b*). This inhibitory action of the vagus on the lung motor mechanism is unilateral. It requires relatively strong tetanization of the peripheral vagus to return the lung to the degree of tonus present when the brain is intact and functioning, and even these strong vagi stimulations usually fail to completely abolish the hypertonus at the apical third of the lung. It is obvious that this is not due to any failure of inhibitory vagi fibers to reach that part of the lung in sufficient numbers, but to the failure of the vagus tetanization to imitate, in rate and intensity, the tonic inhibitory impulses passing from the

[1] The tracings in this article are reduced to about ⅔ of the original.

brain to the lungs, because as long as the vagi and the medulla are intact there is no hypertonus in the lung apex.

We have been unable to show the presence of lung motor fibers in the vagi. As in necturus and axolotl, the lungs of cryptobranchus appear to be provided with inhibitory nerves only.

3. It was pointed out in the case of necturus and axolotl that after opening the abdominal cavity there is stasis of the circulation, or at least an extremely slow circulation, in the visceral organs, including the lungs. We noted that this condition was not due to loss of blood or failure of the heart. This visceral circulatory stasis is also seen in cryptobranchus under the same experimental conditions.

In one animal we attempted to improve the circulation in the viscera by supplying a greater quantity of circulating fluid. We injected slowly 10 cc. of Ringer solution into the hepatic vein. This did not

Fig. 2. Tracing of intrapulmonic pressure of cryptobranchus. Animal immobilized by tying tubber bands around front legs. Lungs exposed by median ventral incision. Tracheal sac ligated. Cannula in tip of right lung. Signal, slow injection of 10 cc. Ringer's solution into hepatic vein. Showing initiation of a temporary lung rhythm, probably of central origin, as similar injections do not produce lung rhythms after destruction of the medulla.

improve the visceral circulation, but induced a temporary rhythm in the lungs (fig. 2). This rhythm was not associated with respiratory movements (swallowing). It was evidently due to central or brain action, as similar intravenous injections fail to induce a lung tonus rhythm after destruction of the brain.

4. Attempts at swallowing air (respiratory acts) are followed by temporary lung contractions in cryptobranchus, similar to those previously described by us in the frog and axolotl. This lung reaction following attempts at forcing air into the lungs by swallowing was never seen in necturus. In the frog and axolotl the primary lung effect of the respiratory act of swallowing is inhibition, and this inhibition is followed by lung contraction. This primary lung inhibition (tonus relaxation) was not seen in cryptobranchus, probably because having only a few animals at our disposal we did not succeed in developing a sufficiently delicate technique for demonstrating it.

Lung reflexes. 1. In the animal partially immobilized with a small dose of curare, stimulation of cutaneous and visceral sensory nerves caused reflex lung contractions (fig. 3). Such contractions were induced by mechanical and electrical stimulation of the skin, the toes, nares, etc., by mechanical stimulation of the anus, by electrical stimulation of the large and small intestines, the urinary bladder and the peritoneum.

All the stimulations that induced reflex lung contractions caused at the same time cardiac inhibition, except the mechanical stimulation of the nares. Electrical stimulation of the ovarian mesentery gave reflex inhibition of the heart, but no contraction of the lungs.

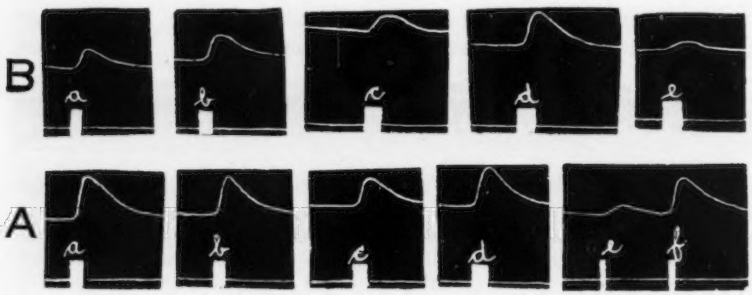

Fig. 3. Tambour records of the intrapulmonic pressure of the right lung of cryptobranchus. Animal curarized one hour previously. "Trachea" and left lung ligated off. Cannula in tip of right lung.

A: a, electrical stimulation of toes; *b*, electrical stimulation of leg; *c*, mechanical stimulation (pinching) of tail; *d*, mechanical stimulation of right nares; *e* and *f*, cutting of skin of anterior abdominal wall over bladder.

B: a, electrical stimulation of bladder; *b*, electrical stimulation of small intestine; *c*, electrical stimulation of large intestine; *d*, electrical stimulation of the intestinal mesentery; *e*, mechanical stimulation of the anus.

Showing in series *A* lung reflexes evoked by the stimulation of various cutaneous nerves; in series *B*, lung reflexes induced by stimulation of various visceral nerves.

In no instance did the visceral or cutaneous stimulations cause relaxation of the lung tonus. In the probable absence in this species of a motor nervous mechanism connecting the lungs with the central nervous system such reflex lung inhibition could have come about by an increase in the central tonus inhibition maintained by the animal in the absence of these artificial stimulations. It is obvious that, in

case this central inhibitory tonus playing on the peripheral lung motor mechanism is maximal under our experimental conditions, sensory stimulation can induce no further tonus relaxation in the lungs.

2. If the interested reader will refer again to our articles on the lung automatism and the lung reflexes in the frog (2), and in the reptiles (3) it will become manifest that the following similarities and differences in lung motor control appear in these animal groups:

a: Central nervous control. In the reptilia this is predominantly, if not exclusively, motor. In the frog it is predominantly inhibitory but also partly motor. In the salamanders it appears to be exclusively inhibitory.

b: Peripheral automatism. In the frogs and the salamanders the peripheral lung automatism is so greatly developed that on release of the lungs from the central inhibitory control (section of vagi, or pithing of medulla) the lungs pass into permanent tetanus, while in the reptilia the lung automatism depends primarily on the motor impulses via the vagi, so that on pithing the brain, or section of the vagi, the lungs become essentially atonic and quiescent.

c: Correlation with respiratory movements. In the reptiles, frogs and salamanders (excepting necturus) the external respiratory act leads to lung inhibition followed by lung contraction. This primary lung inhibition is brought about, in the reptiles, by inhibition of the lung motor center in the medulla; in the frogs essentially and in the salamanders entirely by stimulation of the lung inhibitory center in the medulla. The subsequent lung contraction is brought about, in the reptiles, by stimulation of the lung motor center, in the frog and the salamander by inhibition of the lung inhibitory center, permitting the peripheral lung automatism to come into play.

d: Mechanism of the reflexes into the lungs. Various types of visceral and cutaneous stimulations cause similar reflex lung contractions in the three animal groups. These sensory stimulations induce the lung contractions in the reptile by stimulating the medullary lung motor center, in the frog essentially and in the salamanders solely by inhibiting the medullary lung inhibitory center, so that the peripheral lung automatism is rendered free to act.

These are striking illustrations of similar or identical physiological reactions being brought about by fundamentally dissimilar nervous mechanisms. In amphibia the lung motor impulses originate in the lung tissues, in reptilia the lung motor mechanism has shifted to the medulla, and parallel with this change is the change in the action of

the efferent nerve fibers connecting the brain with the lung musculature. Despite these changes the motor correlation of the lungs with the external respiratory act, and with cutaneous and visceral afferent impulses remain the same.

These facts recall a similar change in the mechanism of the motor control of an organ taking place during the life of the individual. It was shown years ago by one of the authors that in the horseshoe crab (Limulus) the heart automatism resides in the heart ganglion, not in the heart muscle (4). Subsequently it was found that in the Limulus embryos the heart beat starts and shows perfect coördination before any nervous tissue can be recognized in it (5). In other words, in Limulus the heart beat starts as a muscular automatism, and shifts during development to a nervous automatism without change in function or external reactions of the heart as a whole.

The differences in the lung motor mechanism referred to above, occur, to be sure, in the adult state of two quite separate phyla, but if the principle that ontogeny repeats phylogeny is essentially correct, we would expect to find the most primitive or amphibian type of lung motor mechanism at some stage in the embryonic development of reptiles, birds and mammals.

Necturus

1. In a previous report of motor control of the turtle's lung (3), it was pointed out that stimulation of the optic lobes, in confirmation of the work of Coombs (6), caused in this animal marked contractions of the lung. It seemed desirable to determine whether the higher centers of necturus likewise made physiological connection with underlying lung motor centers. Tracings *A* and *B* of figure 4 show that such is the case. Stimulation of the cerebral hemispheres (*A*, *a*), of the optic lobes (*A*, *b*, *B*, *a*), as well as mild tetanization of the medulla (*A*, *c*; *B*, *b*) leads to a lung contraction. The interesting feature of the contractions effected by this stimulation lies in the fact that lung contraction results from the operation of a mechanism quite different from the mechanism effecting a contraction of lung from the stimulation of the same structures in the turtle. In the latter (turtle) the higher centers make apparently motor connections with the lung motor center in the medulla which in turn sends motor impulses to the lung musculature via the vagi; in necturus, on the other hand, the higher center sends impulses to the lung motor center which effect an *inhibition* of the tonic activity of the inhibitory lung motor center allowing the lungs to

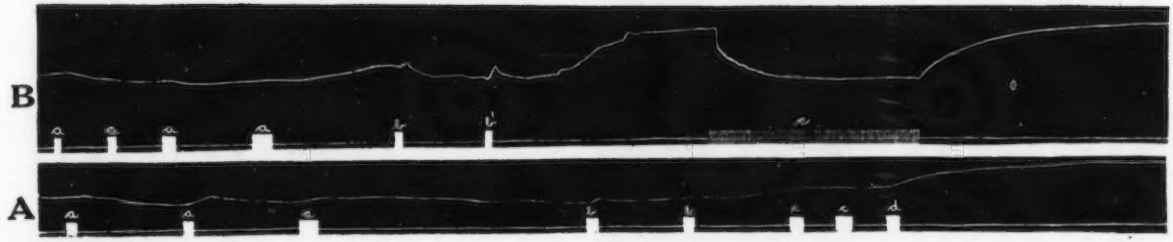

Fig. 4. Water manometer tracings of the intrapulmonic pressure of necturus. Spinal cord sectioned and pithed below the medulla. Animal on ventral side. Brain exposed without injury. Cannula in tip of left lung. Communication of this lung with the other and with oral cavity prevented by pressure applied over the tracheal sac. Unipolar method of stimulation used throughout.

A: a, electrical stimulation of the cerebral hemispheres; at *b* and *b*, electrical stimulation of the optic lobes; at *c*, electrical stimulation of the medulla; at *d*, electrical stimulation of the medulla with a stronger current.

B: a, electrical stimulation of the optic lobes; at *b* and *b'* electrical stimulation of the medulla with a tetanizing current; at *c*, electrical stimulation of the medulla at intervals, as indicated, with a tetanizing current.

Showing a slight temporary escape of the lung from the normal inhibitory control of vagus nerve on stimulation of the cerebral hemisphere and optic lobes and medulla. Also the permanent hypertonus resulting from strong stimulation of the medulla itself (physiological disorganization of the lung motor center) and the complete inhibition of the lung on stimulation of the medulla near the exit of the vagus nerve.

escape temporarily from this inhibitory control. The result of the stimulation of the higher centers of the turtle and necturus is the same, namely, a contraction of the lung; the mechanism which leads to the temporarily contracted state of the lung is entirely different.

Moderately strong stimulation of the medulla of necturus leads, on the other hand, to a physiological disorganization equivalent to destruction of medulla by pithing. As a result the lungs escape from their central inhibitory control and assume the hypertonic state characteristic of the unopposed activity of peripheral automatic motor mechanism. These points are illustrated in figure 4, *A*, at *d* and *B*, at *b'*.

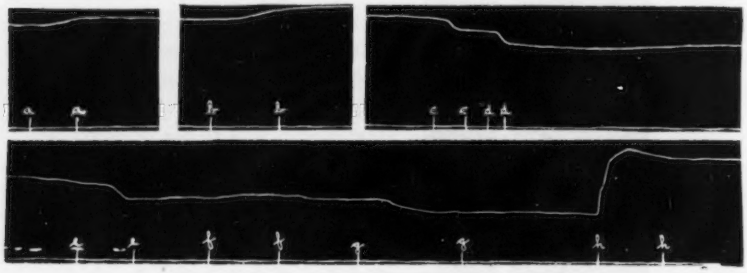

Fig. 5. Tracing of the intrapulmonic pressure in necturus. Spinal cord and brain pithed. Glottis closed. Cannula in tip of right lung. Left lung ligated at base. Right lung in state of permanent tetanus as result of pithing of medulla. Irrigation of surface of right lung with Ringer's solution. *a–a*, Ringer at 22°C. (room temp.); *b–b*, Ringer at 38°C.; *c–c*, Ringer at 52°C.; *d–d*, Ringer at 52°C.; *e–e*, Ringer at 52°C.; *f–f*, Ringer at 22°C.; *g–g*, Ringer at 60°C.; *h–h*, Ringer at 82°C.

Showing inhibition of the lung tetanus by temperatures below that which induces immediate heat rigor of the lung musculature.

Stimulation of the peripheral end of the vagus effects a prompt and maximal dilatation of the lung lasting throughout the period of stimulation as is illustrated in figure 4, *B*, at *c*. There is also seen an unusually quick return to the previous hypertonic state on the cessation of the stimulation.

2. As stated earlier in this article, pituitrin has no noticeable effect on the musculature of the lung of necturus irrespective of the mode of administration. We therefore attempted to induce pulmonary contractions by applying here and there to its surface a few drops of a 1 per cent solution of barium chloride, a well recognized stimulant of smooth muscle. But neither the direct application nor irrigation of

the lung with this strong solution had the slightest effect on the lung. The same solution applied to the exposed stomach or intestine of an etherized dog caused prompt and powerful local contractions in these viscera.

The inability to cause contraction of the smooth musculature in the lung of necturus by the drug, $BaCl_2$ which, according to Dixon (7), stimulates all types of muscle so readily that it may be used to detect the presence of musculature in various organs or viscera, lead to the suggestion that possibly the smooth musculature might be affected by heated Ringer's. The results obtained from the irrigation can be seen by inspecting figure 5. Ringer's solution heated to 22°C. and 38°C., caused a further contraction of the hypertonic lung (*a-a* and *b-b*). At 52°C. and at higher temperatures Ringer's solution caused a typical and pronounced inhibition from which there was practically no recovery (*c-c*, *d-d*, *e-e*, *g-g*). Irrigation of the lung with Ringer's solution heated to 82°C., effected an immediate heat coagulation of the protein (*h-h*).

The interpretation of the results with Ringer's solution heated to different temperatures is not clear. At lower temperatures (22°, 38°) the peripheral automatic mechanism is stimulated, leading to an increase in hypertonic condition of the lung. As the temperature of Ringer's solution is raised, inhibition of the lung results due either to direct stimulation of the inhibitory fibers of the vagus or to heat paralysis of the nervous mechanism in the lung responsible for the hypertonic state. The failure of recovery might suggest that the latter explanation is the more probable one. But in previous work we found that electrical stimulation of the peripheral vagus resulted many times in an inhibition of the lung from which there was but feeble or no recovery. When the temperature is raised to the point of coagulation of the tissue protein the lung is reduced to the condition of a cord.

It should be noted that the above result represents the immediate effects of pouring the heated Ringer over the lung surface for short periods. It is highly probable that subjecting the lung tissues to high temperatures for longer periods will cause heat coagulation before 82°C.

SUMMARY

1. In cryptobranchus the lungs are kept in a state of practically maximum relaxation by inhibitory impulses reaching them via the vagi from a lung motor center in the medulla; for *a*, destruction of the medulla or section of the vagi nerves promptly induces a more or less

permanent hypertonic state of the lung; and *b*, stimulation of the peripheral end of the vagus causes during the period of stimulation a marked inhibition of this lung tonus.

2. A slight tonus rhythm usually appears in the lungs of cryptobranchus rendered hypertonic by destruction of the medulla or section of the vagi nerves. A temporary tonus rhythm may appear on the intravenous injection of Ringer's solution but only when the medullary center and vagi nerves are intact. This latter rhythm has, therefore, a central origin.

3. In the curarized cryptobranchus stimulation of cutaneous and visceral sensory nerves causes reflex lung contraction and reflex cardiac inhibition with two exceptions: mechanical stimulation of the nares causes lung contraction without cardiac inhibition,—electrical stimulation of the ovaries and ovarian mesentery causes reflex cardiac inhibition but no lung contraction.

4. Electrical stimulation of the cerebral hemispheres, optic lobes and medulla of necturus causes lung contraction by an inhibition of the inhibitory lung motor center. Strong stimulation of the medulla induces a permanent hypertonic state of the lung. Such stimulation is equivalent to destruction of the medulla or section of the vagi.

5. The irrigation of the lung of necturus with even a strong solution of barium chloride has no effect on the smooth musculature of the lung. We have obtained the same negative result with pituitrin and histamine, drugs which, like barium, supposedly stimulate smooth musculature by direct action. Adrenalin chloride applied to the lung surface is also without effect on the lung tonus.

7. Ringer's solution at room temperature or heated to 38°C. causes further muscular contraction of the hypertonic lung. At higher temperatures (52 to 75 degrees) Ringer's solution effects a decided inhibition from which there is no recovery.

NOTE: When the animals were not decerebrated prior to preparation all the incisions were made under local anesthesia.

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A STUDY OF LOW OXYGEN EFFECTS DURING REBREATHING

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The original data of the Air Service, U. S. Army, official altitude classification examination of all aviators who were given this test, have been collected and filed in the Medical Research Laboratory at Mitchel Field on Long Island. There are approximately 7150 cases. From these 1050 have been selected for an analysis of the physiological responses. Some of the characteristic features of the results are here discussed.

The so-called Official Altitude Classification Examination is a low oxygen test in which the aviator is required to rebreathe 52 liters of air from which the carbon dioxide is removed by sodiun hydroxide. The Henderson-Pierce rebreathing apparatus (1) was used in all the examinations. In the routine test the pulse rate and arterial pressure were determined once each minute and the respiration recorded on a kymograph. The kymograph tracing is in reality a record of the movements of the spirometer. This not only records the volume of each breath, but also the reduction in air volume and the oxygen consumed. Throughout the entire period of rebreathing the aviator was busy with work directed by a psychologist (2) whereby the condition of voluntary coördination and attention was observed. The psychologist determined the earliest effects on attention and motor coördination, the time of appearance of more marked effects, and of total breakdown. The experiment was terminated when the subject had reached the point of complete mental inefficiency, or when the circulation indicated oncoming syncope.

The subject of an experiment does not ordinarily experience discomfort. Many of the men show some degree of apprehension immediately prior to and at the beginning of rebreathing. This is evidenced in various ways, by an acceleration of the pulse, a rise in blood pressure or

increased breathing. Once the experiment is well on the evidence of apprehension usually quickly disappears. The discomfort of the nose-clip and mouthpiece bother some men, but even these annoyances pass from the field of consciousness as the low oxygen effects develop. The subject, as a rule, is entirely unaware of any change in his condition even though he may have been carried to unconsciousness. A good reactor, who does not faint, may fail to attend to first one, then another and finally all of the signals directed by the psychologist and sit glassy-eyed, deaf and irresponsive to signals or questions; and yet, when revived with fresh air, ask why he was not carried further. He cannot readily be convinced that he has been unconscious. Even the subjects who develop the fainting reaction are not aware of their condition, and unless they are actually allowed to faint often question the saneness of the observer. After-effects, such as headache, "tightness of head" and lassitude, are sometimes observed. When the subject is allowed to faint complete recovery is as a rule rapid, but has been slow in several instances.

The degree of oxygen deficiency tolerated shows a wide range. Captain J. E. Coover examined 2279 Pre-Armistice cases as to final oxygen per cent and the time required to reach it. The mean for the final oxygen per cent was 7.42 ± 0.01, with extremes of 11 and 5.2 per cent. The mean length of run was 24.65 ± 0.05 minutes, with the extremes 15 and 35 minutes.

THE CIRCULATORY REACTIONS

The response of the circulatory mechanism to the gradual steady decrease in oxygen has been considered by Schneider (3), Lutz and Schneider (4) and Greene (5). We have compiled what may be called the normal and therefore the most frequent type of reaction by calculating the arithmetical means and probable error of the mean for a number of groups of selected cases. Since the curves that show the changes in the pulse rate, the systolic, diastolic and pulse arterial pressures are quite similar for the several groups, the results obtained from one group are here presented in detail. This included 148 cases of the non-fainting type of reaction. The data for these experiments were tabulated and the means for the pulse rate and the arterial pressures calculated for the standing posture, for the seated position taken from the preliminary observation just before the rebreathing was begun, again three minutes after the rebreathing began, and then at the following percentages of oxygen during the experiment: 18, 15, 13, 12, 11,

10, 9, 8 and 7. The last means calculated were those for the first readings after the subject was taken off and allowed to breathe fresh air. The results are shown graphically in figure 1 and are tabulated in table1 .

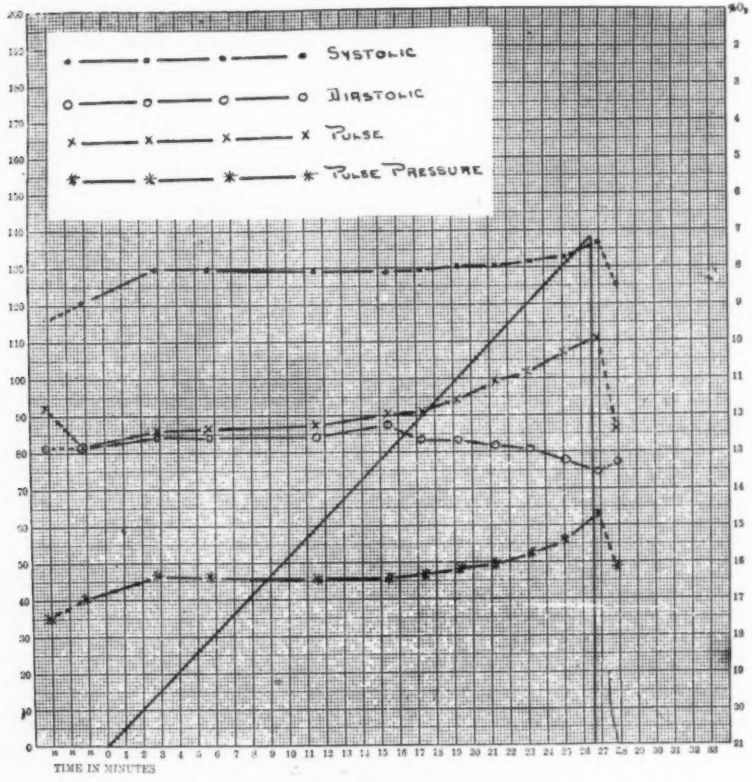

Fig. 1. A normal but composite compensation to low oxygen. The curves were established by calculating the arithmetical means for 148 cases. 1st N—standing. 2nd N—seated. Continuous heavy oblique line = oxygen. Continuous heavy verticle = Mean time at end of test.

It is evident from these data that the majority of all men who undergo the low oxygen rebreathing examination show a psychic reaction that is still in evidence at the third minute in each of the circulatory factors here

studied. This psychic reaction is most conspicuous in the systolic pressure. The curves also show that if a decrease in oxygen down to 19 per cent has any influence upon these circulatory factors, this response is obscured by the psychic reaction.

The composite curve shows that the pulse rate accelerates almost from the first. This acceleration at the beginning is slight and gradual, but from 12 per cent down to the end is more marked. There is a well-defined compensation evidenced by the arterial pressures in the rise in the systolic, and the fall in the diastolic pressures that begin at 12 or

TABLE 1

Means and probable error of mean in 148 non-fainting cases

OBSERVATION	PULSE RATE PER MINUTE	ARTERIAL PRESSURE IN MM. Hg.			NUMBER OF CASES
		Systolic	Diastolic	Pulse	
Standing.....	92.92±0.69	116.51±0.61	81.68±0.47	35.32±0.62	148
Before rebreathing (seated).....	81.83±0.62	121.19±0.62	81.48±0.38	40.32±0.57	148
3 minutes on rebreather....	85.81±0.76	130.32±0.79	84.94±0.42	46.62±0.69	148
18 per cent O_2..	86.09±0.71	130.16±0.79	84.70±0.44	46.08±0.67	148
15 per cent O_2..	87.45±0.70	129.7 ±0.77	84.46±0.44	45.67±0.66	148
13 per cent O_2..	90.08±0.66	129.38±0.73	87.88±0.39	45.95±0.56	148
12 per cent O_2..	91.13±0.66	129.70±0.73	83.92±0.43	46.84±0.58	148
11 per cent O_2..	94.05±0.71	130.46±0.75	83.38±0.40	48.43±0.61	148
10 per cent O_2..	99.49±0.74	130.50±0.75	81.82±0.46	49.58±0.60	147
9 per cent O_2..	101.38±0.73	131.94±0.74	80.38±0.45	52.58±0.64	145
8 per cent O_2..	106.98±0.83	133.17±0.79	77.73±0.47	56.06±0.65	127
7 per cent O_2..	110.74±1.04	137.03±1.02	74.63±0.65	63.20±1.02	70
First reading after off.....	86.43±0.78	125.48±0.69	77.0 ±0.47	48.68±0.60	148

11 per cent and continue to the close of the experiment. The changes in the systolic and diastolic pressure beginning at 13 per cent coöperate to steadily increase the pulse pressure.

Not all of the men endured to as low as 7 per cent of oxygen. Of the 148 cases all reached 11 per cent, while 147 went to 10 per cent, 145 to 9 per cent, 127 to 8 per cent and only 70 to 7 per cent. There were three cases that reached 6 and less—5.8, 5.8 and 5.6 per cent.

The uniformity with which the individual cases of a group make the ordinary circulatory responses to low oxygen is well illustrated by a frequency study. The data for a group of 100 cases of men who toler-

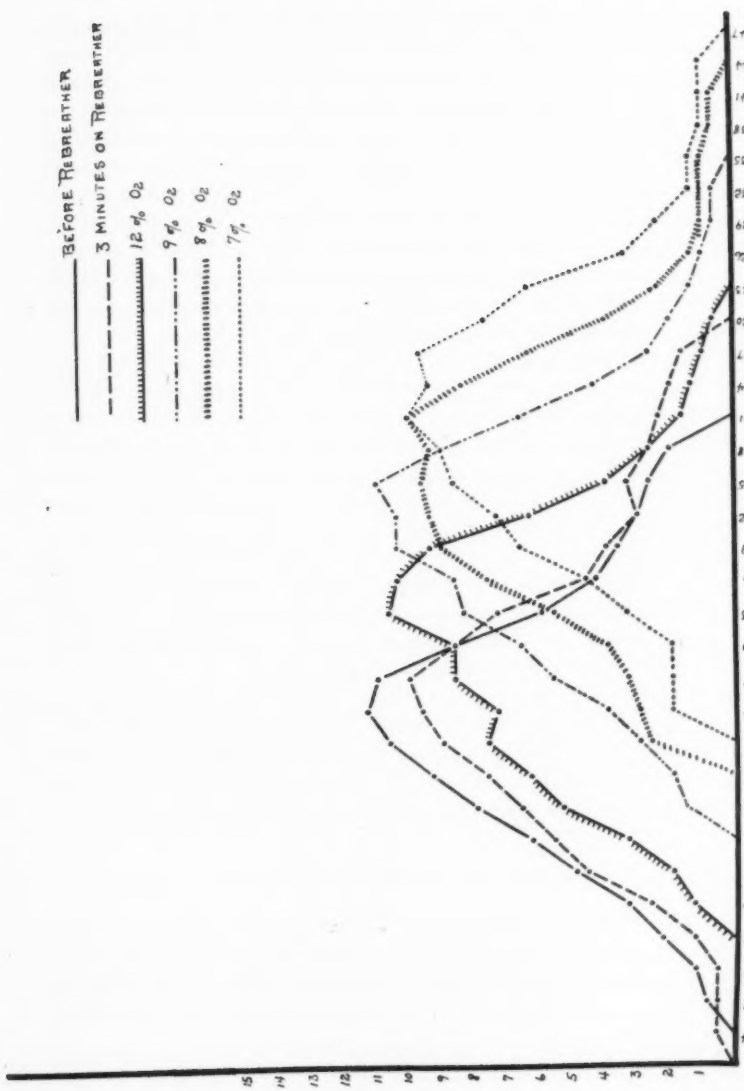

Fig. 2. Pulse rate distribution curves of 100 cases who reached 7 per cent or less of O_2. The base line shows the pulse rate intervals and ordinate the number of cases.

ated to 7 per cent or less of oxygen, were tabulated as to frequency in distribution for the pulse rate and the arterial pressures for the same time intervals and oxygen percentages used to establish the curves of figure 1. The pulse rate frequency curves for six of these periods have been reproduced in figure 2. They show that each man made a good compensation as oxygen want increased, in that there is a shifting of the curves to the right along the base line on which the pulse rate intervals have been marked. The limits, as well as the mode of each curve, shift at 12, 9, 8 and 7 per cent respectively. The mean pulse rate for the group at each of these points was 83.2, 86.4, 90.2, 100.1, 105.5 and 111 respectively. Each of these almost coincides with the respective observation for the group presented in figure 1.

While in the arterial pressures the base line for the curves of frequency becomes longer, due to a scattering of the cases, as the lower oxygen percentages are reached, yet a similar shifting of the curves is present for each factor except the systolic pressure. For the diastolic pressure at the preliminary reading, at three minutes and at 12, 9, 8 and 7 per cent the lower and upper ranges of the respective curves were 54–102, 58–106, 66–102, 62–102, 58–98 and 38–94 mm. The respective means for the several curves were 80.9, 84.6, 84.3, 80.9, 79.1 and 72.9 mm. The diastolic curves, as the oxygen decreases, shift to the left instead of the right because the pressure shows a fall. The diastolic means recorded for this group will be found to be almost identical with those of corresponding percentages in figure 1.

The pulse pressure frequency curves shift to the right along the base line as the oxygen decreases. The lower and upper limits of these, for the same periods used in the pulse rate and diastolic pressure, were 18–82, 14–78, 26–82, 30–90, 30–86 and 34–94 mm. The modes for the respective periods were 42.4, 49.4, 48.6, 54.4, 57.4 and 63.4 mm.

VARIETIES OF CURVES OF REACTION

A number of variations of greater or lesser degree from the ideal curve of response occur in each group of cases that has been examined. These fall more or less sharply into well-defined sub-groups. Some of the outstanding varieties of the curves of response have been assembled in figure 3.

Pulse rate curves. The pulse rate response can be expressed by eight types of curves which in reality occur in four pairs, containing a psychic and non-psychic variation. In variety 1 (see fig. 3) a temporary

initial psychic rise is present, which apparently does not obscure the initial low oxygen acceleration. In 2, there is no initial psychic effect and the low oxygen acceleration begins early, sometimes at once and in all cases before three minutes have elapsed. Variety 2b is much like 2, with an initial psychic rise which has a tendency to disappear, but before its disappearance the low oxygen effect has already begun and the progressive accleration starts at a higher level than in 2. In variety 3, where the psychic influence is lacking, the pulse rate does not change until the oxygen has decreased to 15 per cent or less. Variety 3b is like 3 except that an initial psychic reaction occurs which persists unabated until a late low oxygen effect further accelerates the pulse rate. In varieties 4 and 4b, the initial non-psychic and psychic responses are present as in 2 and 2b; but differ in that toward the end of the experiment, as the limit of endurance is approached, the pulse rate retards, causing a slow or rapid terminal fall in the curve. Curve 1b is characterized by an initial psychic limb and a terminal drop. Occasionally there are cases in which the pulse rate, with and without the initial psychic effect, shows no clearly defined response to the decrease in oxygen. An analysis of the data from 300 aviators, who underwent the rebreathing experiment, gave the following distribution among the pulse rate variety of curves.

1	98 cases =	32 7 per cent
1b	5 cases =	1 7 per cent
2	37 cases =	12 3 per cent
2b	65 cases =	21 7 per cent
3	48 cases =	16 0 per cent
3b	26 cases =	8 7 per cent
4	4 cases =	1 3 per cent
4b	7 cases =	2 3 per cent
No response or uncertain	10 cases =	3 3 per cent
Total	300 cases =	100 0 per cent

Systolic pressure curves. The varieties of curves for the systolic arterial pressure can be grouped among eight patterns, some of which are diagrammed in figure 3. In variety 4, the systolic pressure remains constant with exception of irregular fluctuations throughout the low oxygen experience. Variety 4b differs from 4 in the presence of an initial psychic rise, which after several minutes of rebreathing wholly disappears. In 5 there is also, as in 4, no evidence of compensation, the systolic pressure remaining constant until toward the end of the

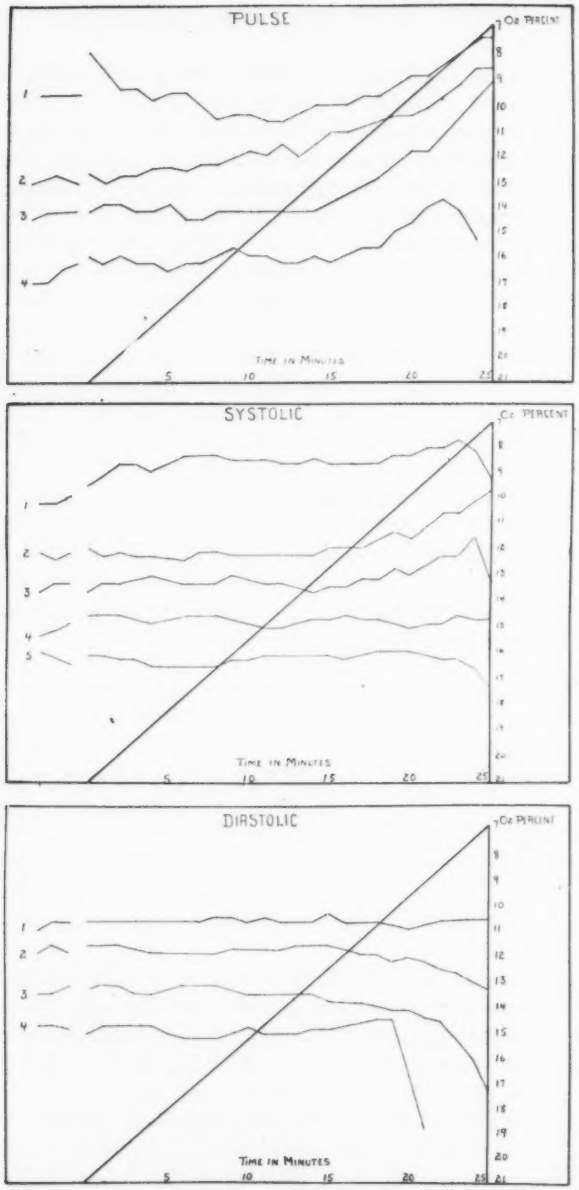

Fig. 3. Curves illustrating the varieties of reaction for each circulatory compensatory factor. The diagonal line indicates the rate of oxygen change.

experiment when it begins to fall with different degrees of rapidity. In varieties 1, 2, 2b, 3 and 3b, evidence of compensation is found in the occurrence of a terminal rise; this rise occurring as early as 15 per cent oxygen in some cases, but more frequently at a lower oxygen. Variety 2 is without, while 2b has an initial temporary psychic rise. In 1 there immediately occurs a sharp rise in the systolic pressure that persists throughout the rebreathing, toward the end there is some degree of compensatory rise; but still later there is a fall, which continues until the subject faints or is given fresh air. Varieties 3 and 3b correspond to 2 and 2b respectively, with a difference in the terminal part of the curve in which, after some degree of compensatory rise, the systolic pressure falls more or less rapidly.

The distribution of 300 cases among eight varieties of systolic pressure curves follows:

1	80 cases =	26.7 per cent
2	32 cases =	10.7 per cent
2b	68 cases =	22.7 per cent
3	6 cases =	2.0 per cent
3b	14 cases =	4.7 per cent
4	23 cases =	7.7 per cent
4b	9 cases =	3.0 per cent
5	68 cases =	22.7 per cent
Total	300 cases =	100.2 per cent

Diastolic pressure curves. The diastolic pressure changes do not show as great a variety of patterns as do the changes in pulse rate and systolic pressure. There are five types of curves (see fig. 3) that are found to fit all except very exceptional cases. A small proportion, variety 1, either with or without a brief initial psychic rise in diastolic pressure, holds a fairly constant level throughout the test, giving no evidence of a compensation in this factor of circulation. In 2 and 2b occur the majority of all cases. The two curves are quite alike except in the initial phase, 2b does and 2 does not show a psychic rise at the beginning of the test. In both there is ordinarily present a middle period of increased pressure, but the striking feature is the gradual compensatory fall in the pressure which usually begins after 15 per cent oxygen has been reached and continues slowly falling in a controlled manner to the end of the test. In variety 3 the initial psychic rise is usually present in slight degree while the terminal fall is very marked, called an uncontrolled drop. Variety 4 is one in which the diastolic pressure maintains the initial level until the low oxygen effect appar-

ently becomes overpowering when, without warning, it suddenly falls to a very low level as the subject faints. It is evident from curves 2, 2b, 3 and 4 that under the influence of low oxygen the diastolic pressure ordinarily falls, the curves differing chiefly in the rate of fall.

The pulse pressure curves are of course determined by the changes that occur in the systolic and diastolic pressures and can, therefore, be visualized from these curves. The curve for pulse pressure given in the composite curve in figure 1 is typical for all the groups of cases studied.

In 300 cases the varieties of diastolic responses were grouped as follows:

1	18 cases =	6.0 per cent
2	93 cases =	31.0 per cent
2b	77 cases =	25.7 per cent
3	74 cases =	24.7 per cent
4	38 cases =	12.7 per cent
Total	300 cases =	100.1 per cent

The curves as presented in figure 3 have been partly smoothed. Often an individual original curve is quite saw-toothed in appearance. Some of the variations that give the irregularities are associated with respiration, others are undoubtedly influenced by mental conditions. Occasionally a response does not conform to any of the patterns; most of such cases have appeared to us to lack physiological significance. The demarcation of the varieties is not always clear, one form of curve gradually changing into another by reactions that may be called transitional.

RESPIRATORY CHANGES UNDER THE PROGRESSIVE DECREASE OF OXYGEN

In order to establish the ideal or composite curve for the respiratory changes, analyses have been made of two groups of cases. In the first study the kymograph tracings of 136 cases were checked up as to the per-minute volume, depth and rate of breathing; in the second study of 60 cases (see table 2) in which the volume of breathing was recorded by means of the Larsen respiration automatic recorder and counter, for each minute of the period of rebreathing, the ideal curve and varieties of curves were established. For each group the mean and probable error were calculated for a sufficient number of points to establish the form of the curves. The composite curves derived for the two groups appear in figure 4 and summaries in table 2.

Per-minute respiratory volume. Curve 1, figure 4, was prepared from the group of 60 cases. Unfortunately the method of recording respiration does not permit the determination of either a preëxperiment normal or the postexperiment recovery. Therefore, it has not been possible to indicate the psychic reaction as was done for the circulatory studies. Eleven points in the curve, the same used for the circulatory data, were calculated. The calculation of additional points, which would be permitted by available data, would not add definiteness to the part of the curve that indicates the beginning of the low oxygen effect, since the change is at first so slight that it is almost always debatable. Interpretation and opinion are quite likely to be biased as regards what constitutes an increase. There are, no doubt, two factors other than low oxygen effects that may cause the upward trend in the curve during the first three or more minutes. At first the mental factor enters because of anxiety when the subject begins to breathe the confined air so that for awhile both the rate and volume of breathing may be greater than normal. The mental effect as a rule subsides wholly or partially within three or four minutes. The second factor that may account for a part of the increase in the per-minute volume of breathing is the physical work required in attending and reacting to the psychologist's signals. Just how much this work would increase metabolism has not been determined. However, as the work done remains constant throughout the period of rebreathing its influence on the per-minute volume of breathing would quickly reach and maintain a level. The ascent in curve I, figure 4, up to the third point, 18 per cent oxygen, an interval in time of almost six minutes, represents an increase of 440 cc. in the per-minute volume of breathing. Between 18 and 15 per cent, an interval of five minutes, the increase in breathing is only 90 cc. It seems, therefore, that the increase up to 18 per cent of oxygen can not properly be attributed to the decrease in oxygen. Down from 15 per cent oxygen the per-minute volume of breathing steadily increases as the available oxygen decreases.

Curve II (fig. 4) was derived from the data of 136 cases. The first two points determined for this curve were at approximately 19 and 16 per cent oxygen. The per-minute volume differs between the two points by only 30 cc. This confirms the observations in curve I. Between 19 and 15 per cent there normally occurs a plateau or maintained level in the volume of breathing. In both curves I and II, from between 16 and 15 per cent oxygen, the per-minute ventilation clearly begins to increase. The increase at 7 per cent was greatest in the

group of 136 cases, being 3950 cc. for the group of 60 cases and 5490 cc. for the other.

It should be noted that some men begin very early to respond to the decrease in oxygen. Schneider (3) reported that "in a few men this increase in lung ventilation begins with the first decrease in the oxygen percentages of the air breathed and is a gradual proportional increase

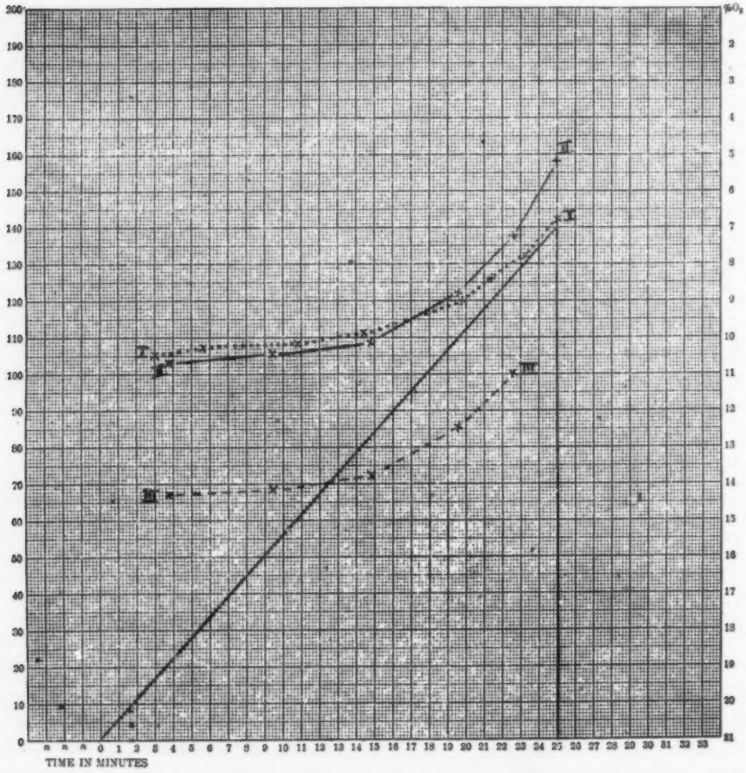

Fig. 4. Composite respiration curves obtained by computing the arithmetical means. *I* and *II*, the per minute volume in deciliters of breathing for 60 and 136 cases respectively; *III*, the depth of breathing (the ordinate on the left should be multiplied by 10 to obtain correct volume in cc.). Continuous oblique line = oxygen percentage; vertical continuous line = length of rebreathing experiment.

to inverse ratio with the reduction in oxygen." Ellis (6) found in a careful study of the problem that there was an increase in the respiratory volume at an average of 18.1 per cent oxygen in 23 of 29 subjects. Lutz and Schneider (7) approached the problem by determination of the alveolar air composition in carbon dioxide and oxygen as well as the per-minute respiratory volume and found in the majority of cases a definite increase in ventilation at oxygen tensions equally as low as those reported by Ellis.

TABLE 2

Mean volume of respiration during rebreathing

GROUP I				GROUP IIA			
Oxygen	Number of cases	Per-minute volume	Probable error	Oxygen	Number of cases	Per-minute volume	Probable error
per cent		*cc.*	*cc.*	*per cent*		*cc.*	*cc.*
20.96	60	10,275	200	18.9	150	10,320	137
19.5	60	10,525	184	15.8	150	10,353	161
18.0	60	10,717	204	12.7	150	10,873	178
15.0	60	10,808	219	10.0	146	12,226	211
13.0	60	11,117	250	8.4	112	13,759	312
12.0	60	11,350	254	7.0	6	15,833	1302
11.0	60	11,600	230				
10.0	60	12,017	227				
9.0	56	12,629	232				
8.0	44	13,234	198				
7.0	15	14,233	612				

In group II there were 91 men who reached 8 per cent or less of oxygen. The average increase in the per-minute volume of ventilation was 4990 cc.; the greatest was 21,400 cc., and the least was 450 cc. There were 37 men who lasted only to between 10 and 8.1 per cent; their average increase was 340 cc., the largest 890 cc. and the smallest 100 cc. Not a man in this group of 136 cases wholly failed to make a respiratory response. In group I, 60 cases, there were 5 who failed to respond to the low oxygen, while the greatest response was only 10,700 cc.

The largest per-minute volume of breathing observed among 97 men who tolerated less than 8 per cent oxygen was 39,500 cc., and the smallest 820 cc.

By means of frequency curves the distribution of cases as to per-minute volume of breathing at the beginning and end of the rebreath-

ing test has been shown for a group of 160 cases in figure 5, the bottom curves. The curves illustrate the normal shifting of the curves to the right as compensation occurs. The mode moves from between 8000 and 8999 cc. for the "beginning" curve, to between 11,000 and 11,999 cc. for the "end" curve. The range or limits of the curves also show a similar shift of position.

Depth of breathing. Not alone is compensation to low oxygen shown in the volume of air breathed per minute, but the volume of each individual breath also is usually increased. The average increase has been determined by calculating the mean increase for 136 men and is plotted in curve III of figure 4. These data are tabulated in greater detail in table 3. They show an average increase at 8.4 per cent oxygen

TABLE 3

Depth of breathing under low oxygen

	OXYGEN	NUMBER OF CASES	MEAN VOLUME PER BREATH	INCREASE OVER A	RATE PER MINUTE
	per cent		*cc.*		
A	18.9	138	670±10		16.4
B	15.8	138	683±11	13±14	16.0
C	12.7	138	723±14	53±17	15.9
D	10.0	134	855±16	185±18	15.5
E	8.4	100*	999±25	329±26	15.0

* Mean of A for these 100 cases 657±12 cc.

of 329 cc., or 49.1 per cent in the volume of each breath. These means show that there is an early increase in the depth of breathing, before 16 per cent of oxygen is reached. Not all the men gave the increase in depth of breathing, 9, 6.6 per cent, had a decrease in depth but increased the per-minute volume by increasing the rate of breathing. All other cases, that is 127, or 93.4 per cent, had the increase in depth. Of the 91 who went to less than 8 per cent oxygen, 7 had a decrease in depth of from 100 to 380 cc., average 130 cc.; and the other 84 had an average increase in depth of 450 cc. The greatest increase observed among these men was 1660 cc., in this case the volume per breath during the first minute of rebreathing was only 520 cc. The greatest volume per breath observed during regular breathing was seen in a man who inspired 2370 cc., but at the beginning of the experiment each breath was already 1010 cc.

Frequency curves that show the distribution of cases as to volume of the individual breaths are given in figure 5 (upper section) for 138

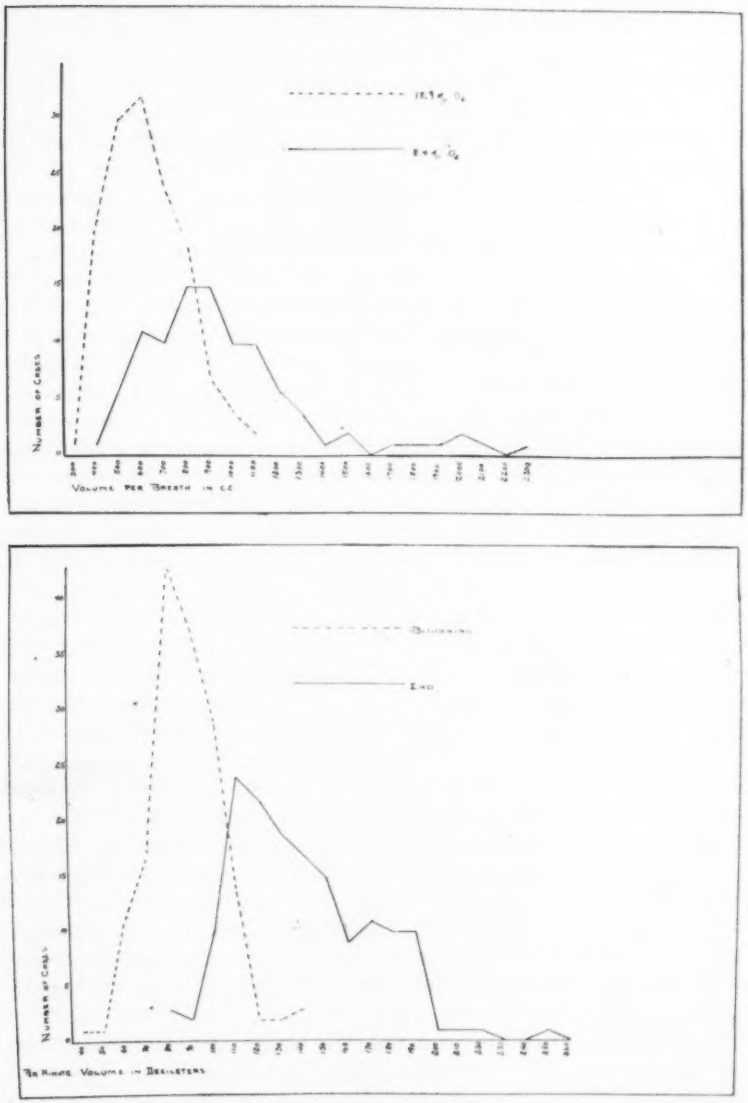

Fig. 5. Frequency respiration curves at the beginning and end of rebreathing. Above—mean depth of breathing in cubic centimeter for 138 cases. Below—mean per-minute volume in deciliters for 136 cases.

cases at 18.9 per cent oxygen, and again at 8.4 per cent for the 100 wh. managed to go that low. The ranges in the two curves show a definite upward movement for the entire group that reached the lower oxygen. At 18.9 per cent oxygen the smallest volume per breath was 380 cc., the maximum 1160 cc.; at 8.4 per cent the smallest was 460 cc. and the maximum 2370 cc.

Rate of breathing. Low oxygen influences the rate in two directions. In the group of 136 cases the rate decreased in 75 or 55.1 per cent, increased in 43 or 31.6 per cent and was unchanged in 18 or 13.3 per cent. The mean rate of breathing for the group at 18.9 per cent of oxygen was 16.4 breaths per minute, at 15.8 per cent 16 breaths, at 12.7 per cent 15.9 breaths, at 10 per cent 15.5 breaths, and at 8.4 per cent 15 breaths. The influence upon rate may, therefore, manifest itself by either an increase or decrease in men who react best to the low oxygen of rebreathing. Among the 91 who went to below 8 per cent oxygen, there were 32 who showed an increase and 59 a decrease. The greatest increase in rate was 7 breaths per minute, the average 2.8 breaths, and the greatest decrease was 11 breaths averaging approximately 4.5 breaths. Increased rate of breathing may or may not be associated with an increase in the depth of breathing, but a slowing in the rate has always had an increase in the depth of breathing associated with it. By this means a fair respiratory compensation to low oxygen may be made without an increase or but little increase in the amount of air breathed per minute. By this method more air passes the dead space at each breath and the alveoli undergo better ventilation. Several examples selected from the group of cases under consideration will illustrate this. In one the rates at the beginning and at the end of the experiment were 15 and 10, the per-minute volumes 8900 and 9700 cc., and the depth of breathing 590 and 970 cc. respectively. In another for the corresponding periods the rates were 12 and 8, the per minute volumes 9150 and 9750 cc., and the volumes per breath 762 and 1219 cc. respectively.

In our group of 136 cases the slowest rate recorded at the beginning of the test was 9 breaths per minute, at the end 6; the most rapid rate at the beginning 26, and at the end 27. In no instance was the rate of breathing very rapid.

It is apparent from our data that the respiratory compensation to low oxygen may be accomplished in several ways. Even when the per-minute volume of breathing is increased by equal amounts in a group of cases it does not follow that alveolar ventilation is equally

improved in each case. In some instances the per-minute volume increase has wholly resulted from an increase in the rate of breathing, in others the rate of breathing has not changed, but the depth has increased, and in still others the rate has decreased while the depth increased in greater proportion. It is evident that the alveolar ventilation is greatest in the last, less in the second and least in the first condition. A less adequate compensation, but nevertheless helpful in some degree, is that in which, although the per-minute volume does not increase, the depth of breathing is materially increased by virtue of a reduction in the rate.

Varieties of respiratory curves. As with the circulatory reaction so it is with the breathing, men do not all follow the same pattern of response when reacting to the continuous decrease in oxygen during the rebreathing test. There are five curves that ordinarily represent the varieties of response in the per-minute volume of breathing. They have been drawn in figure 6. Each curve was taken from a typical test and has been smoothed. Respiration volume rarely runs a perfectly smooth minute-by-minute course. The kymograph tracing for the early part of the test often shows an occasional breath deeper than the average and in the last minutes when the oxygen is below 9 per cent these increase in frequency and may become deep sighing breaths. Occasionally there are men who show a tendency to a type of rhythmic breathing, quite like Cheyne-Stokes breathing. The minute-by-minute volume of breathing shows such variations that as a regular laboratory procedure the readings are averaged by the usual "smoothing" process advocated in statistical methods. However, the volumes of the first and last minute are plotted just as recorded from the Larsen automatic recorder.

Curve 4, figure 6, represents the non-compensating cases in which a slight psychic initial response is frequently present. The non-compensator usually does not last long. Curve 3 is typical of a moderate respiratory compensation which, not being sufficient, causes inefficiency or failure under 8 per cent oxygen. Variety 2 represents the good response common among men who last to a very low oxygen, 7 to 6 per cent. Curve 1 illustrates the typical psychic initial large volume of breathing which lasts from one to five minutes. After the psychic effect has subsided the curve of reaction may show a good response to low oxygen. Curve 5 illustrates a less frequent variety of response in which there is an earlier and more rapid increase in the per-minute volume of breathing than ordinarily, and later a decrease sufficient to hasten the development of inefficiency or fainting.

The 60 cases that furnished the material for this variety of curves were grouped as follows:

1. Good compensation with initial psychic rise, 17 cases, 28.3 per cent. Average final oxygen, 7.4 per cent.

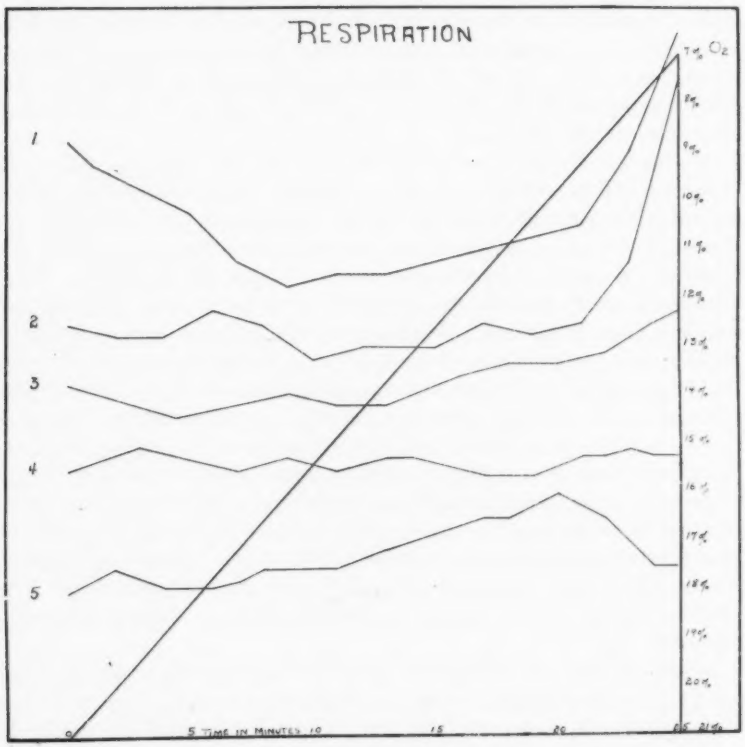

Fig. 6. Curves illustrating the varieties in the per-minute volume respiration response.

2. Good compensation, 25 cases, 41.7 per cent. Average per-minute volume at the beginning, 956 cc., at the end, 1482 cc. Average final oxygen, 7.3 per cent.

3. Slight compensation, 5 cases, 8.3 per cent. Average per-minute volume at the beginning, 900 cc., at the end, 1100 cc. Average final oxygen, 8.3 per cent.

4. No compensation, 5 cases, 8.3 per cent. Average per-minute volume of breath, 910 cc., average oxygen reached, 8.6 per cent.

5. Compensation with terminal decrease, 6 cases, 10 per cent. Final oxygen, 8.1 per cent. In this group were placed three cases in which the per-minute volume of breathing was very large from the beginning and quickly increased to unusual amounts, 17,400 to 28,700 cc. Similar cases have been reported by students of metabolism and attributed to a psychic rather than a physiological action. They are occasionally encountered in the rebreathing work, but not in such proportion as in this group which was selected at random and afterward more carefully scrutinized.

The group contains a higher percentage of respiratory non-compensators than any other we have examined. Two cases have not been placed among the listed variety of responses They showed a large initial psychic effect which required two to four minutes to reach its maximum volume. The psychic effect then only partially subsided after which the per-minute volume of breathing remained constant.

TYPES OF PHYSIOLOGICAL REACTION TO THE SLOW CONTINUOUS DECREASE IN OXYGEN

The experience with rebreathing in the Air Service Laboratories has clearly shown that the central nervous system is not affected in the same manner in all men. Because of this it has been necessary to have the responsibility of determining when the subject should be returned to fresh air divided between two observers: the psychologist, who observes attention and motor coördination; and the clinician, who has the physiological data as his guide. With some men the higher or psychic centers are paralyzed before the vasomotor, cardiac and respiratory centers. Most of these men can be carried into unconsciousness and for at least a few seconds will continue to sit perfectly erect as the heart rate and respiration continue to increase. In several instances such cases have been carried beyond unconsciousness until twitching of the arms and legs preliminary to a loss of muscle tone appeared, and still the respiratory and circulatory mechanisms continued compensatory effort. This is called the non-fainting type of reaction. In other men the circulatory controlling, and sometimes respiratory, brain centers begin to show evidences of incoördination before voluntary attention and motor coördination are markedly affected, or at least before their breakdown occurs. The evidence of impending circulatory collapse is

usually found in a rapid fall in the diastolic pressure; a drop in the systolic pressure, which is later supplemented by a diastolic pressure fall; or in a slowing of the heart rate. In each of these the subject, if not immediately restored to fresh air, rapidly passes into the typical syncope complex and faints. This type has been called the fainting reaction.

A group of 300 cases, who had taken the rebreathing test under the observation of a single physiologist, was selected for a detailed study of their reactions. These men ranged between 19 and 32 years of age, except three who were 34, 39 and 41 years respectively. The mean age for the group was 25.2 years. In weight they ranged from 110 to 194 pounds, their mean weight being 150.7 pounds. There were 160 non-fainting and 140 fainting type cases.

The two types of reactors did not show a material difference as to low oxygen reached or time required to reach it. The non-fainting group became inefficient at oxygen percentages ranging between 10.7 and 5.6. The mean oxygen reached was 7.24 ± 0.05 per cent. The length of the period of rebreathing varied between 17 minutes 40 seconds and 32 minutes and 45 seconds, the mean period being 26.6 ± 0.17 minutes. For the fainting group the final oxygen ranged between 11.1 and 5.8 per cent, with a mean of 7.81 ± 0.06 per cent, only $\frac{1}{2}$ of 1 per cent difference in the means of the final oxygen for the two groups. The time for the fainting group ranged between 17 minutes 17 seconds and 30 minutes 18 seconds with a mean of 25.07 ± 0.16 minutes.

In tables 4 are summaries of the low oxygen reached by the two groups and of the cases removed by the psychologist for mental inefficiency and by the clinicians for circulatory failure or other evidence of approaching syncope. There were 20 in the fainting and only 3 in the non-fainting group who failed to compensate adequately down to 9 per cent oxygen. While only 13 per cent of the fainters tolerated to less than 7 per cent oxygen, there were 45.2 per cent of the non-fainters who held out below that per cent. The psychologist stopped the experiment because of mental inefficiency for only 34.5 per cent of the fainters and for 92.5 per cent of the non-fainters. Just why the clinician removed some of the non-fainters is not clear in all of the records; reasons given were heart irregularities or abnormalities, high systolic pressure and color changes. Among the fainters it often happened that the subject would be working well and be attentive to the signals, but would suddenly cease to do so concomitantly with the development of the circulatory syncope symptoms.

The data of table 4 show clearly that some men become mentally inefficient at only moderately low oxygen (11.5 to 9 per cent) because the compensations are inadequate. The two types of reactors to low oxygen indicate that failure among aviators while flying at high altitudes may result merely because the higher brain centers are inadequately supplied with oxygen, or from fainting caused by the paralyzing action of low oxygen on the vasomotor and cardiac centers.

TABLE 4

Summary of final oxygen per cent for the 300 cases

Final oxygen	NON-FAINTING GROUP				FAINTING GROUP			
	Inefficient		Off by psychologist	Off by clinician	Inefficient		Off by psychologist	Off by clinician
	Number of cases	Per cent			Number of cases	Per cent		
per cent								
11+					1	0.7		1
10–10.9	1	0.6	1		1	0.7		1
9–9.9	2	1.2	2		18	13.0	3	15
8–8.9	21	13.0	12	9	43	30.9	11	32
7–7.9	64	40.1	61	3	58	41.7	25	33
Below 7	72	45.2	72		18	13.0	9	9
Total...	160	100.1	148	12	139	100.0	48	91

Variety of circulatory response within the types. An attempt has been made to find whether certain combinations of the varieties in circulatory responses determined the percentage of low oxygen the subject would tolerate. The non-fainting type was separated into two subdivisions according to the variety of diastolic pressure changes, those in which the pressure gradually fell in the latter part of the test and those in which it maintained a level to the close of the test. The non-fainting gradual diastolic fall included 148 and the maintained diastolic only 12 cases. No clear advantage was indicated for either of these. Of the 12 cases with a maintained level 3 failed between 9 and 8 per cent, 7 between 8 and 7 per cent and 2 below 7 per cent oxygen. This result when compared with the summary in table 4 does not show their tolerance of low oxygen to differ materially from that of the entire non-fainting group of 160 cases.

The fainting type was divided into four subdivisions according to the first appearance of evidence of the oncoming syncope. There were

61 cases in which the systolic and diastolic pressures fell together, 45 cases in which the diastolic pressure alone first began a rapid fall, 29 cases in which the systolic pressure began a rapid fall before the diastolic pressure, and 4 cases in which the beginning of the faint was first evidenced in a slowing of the heart rate. The means for the final oxygen reached by these groups were close together; it was 8.2 ± 0.08 per cent for the group in which the systolic and diastolic pressures fell together, 7.66 ± 0.08 per cent for that in which the diastolic, and 7.9 ± 0.13 per cent for that in which the systolic drop first appeared. While the means do not show a large difference, they do give indication of a difference which shows more clearly when the number of cases that failed to reach 8 per cent oxygen are listed. In the group in which the systolic and diastolic pressures fell together, 60 per cent; in the group of systolic fall first, 48.3 per cent; and in the group of diastolic fall first, 33.3 per cent of all cases failed to reach 8 per cent oxygen. In the non-fainting group only 14.7 per cent of the cases failed before 8 per cent oxygen was reached. Apparently in those cases where the systolic and diastolic pressures fall together the effect of low oxygen is the more overpowering.

The percentage of oxygen and the time at which the fall in the systolic and diastolic pressures and the slowing of the pulse rate begin have been determined. A gradual systolic pressure fall occurred in 63 cases. In all of these after falling at the rate of 2, 3 and 4 mm. per minute there was a sudden drop of as much as 5 to 58 mm. per minute. If the fall is as much as 5 mm. in a minute the observer must watch his subject very closely and be ready to restore him to fresh air. Two examples will illustrate a common experience; the systolic pressure in one case gradually fell from 116 to 110 mm. in four minutes, falling to 104 mm. in the next minute and before another determination could be made the man had fainted. Another case gave the following systolic pressures in five consecutive minutes: 132, 130, 128, 126 and 120 mm., and then fainted. A case in which quick action should have been taken gave the following systolic pressures during the last minutes of the test: 138, 138, 80 and 68 mm. If the observer is watchful, ordinarily the subject can be restored without actually fainting. In the 63 cases in which the systolic pressure began to fall gradually, the fall was first observed between the 15th and 27th minutes, the mean time being 21.5 ± 0.25 minutes. The rapid fall in the systolic pressure appeared between the 17th and 29th minutes; the mean was 23.9 ± 0.2. As a rule then the observer had a warning of what to expect for at least

two minutes. The oxygen at the time the gradual fall began ranged between 12.9 and 7.5 per cent, with a mean of 10± 0.09 per cent; and when the rapid fall appeared it ranged between 11.7 and 6.3 per cent, with a mean of 8.9±0.7 per cent. The subgroups of the fainting type conform with the larger group in the onset of the gradual and rapid falls in the systolic pressure.

Among the fainting type there were 101 cases in which a gradual diastolic pressure fall occurred. This first appeared somewhere between the 13th and 27th minutes and changed to a rapid fall some time between the 15th and 29th minutes. The mean time for the appearance of the beginning of the gradual fall was 20.8±0.22 and for that of the rapid fall 23.5±0.18 minutes. A good example of the diastolic fall is one in which the consecutive readings made at minute intervals toward the end of the test were respectively 88, 86, 86, 84, 80, 78, 70, 60 and 40 mm. In such cases the observer has an ample warning of approaching syncope in the diastolic pressure. The gradual fall in the 101 cases began somewhere between 14.7 and 7.5 per cent of oxygen and changed to a rapid fall between 11.7 and 6.6 per cent oxygen. The mean oxygen for the onset of the gradual fall was 10.5±0.09 and for the rapid fall 8.8±0.06 per cent. The diastolic on the average precedes the systolic pressure fall by about a minute. There were 148 cases of the non-fainting type of reactors that showed the gradual diastolic pressure fall. The time of its onset was between the 11th and 29th minutes, with a mean of 20.2±0.2 minutes. The fall began in these cases between 15.3 and 7.5 per cent of oxygen, the mean being 10.7±0.09 per cent. The means for the fainting and non-fainting types are, therefore, practically the same. The gradual diastolic pressure fall is in reality a measure of a normal compensatory reaction to the decreasing oxygen supply.

A slowing of the pulse rate occurs in some men at the end of the rebreathing low oxygen test. In the group of 300 men this occurred 23 times. It began at various times between 10.5 and 6.9 per cent of oxygen. Gilbert and Greene, in papers not yet published, have studied some similar cases by means of the electrocardiograph and find that the slowing of the heart and heart irregularities do not ordinarily appear until the stage of oxygen want is insufficient to maintain the nervous system in conscious activity. They show that a cardiac crisis, during low oxygen, is imminent at the approach of unconsciousness. They were not able to definitely determine whether the slowing is a vagus inhibition due to action of low oxygen on the cardio-inhibitor center, or whether

it is a direct oxygen want effect upon the heart pace-making tissue. In four of our cases the heart began to slow before other evidence of syncope appeared. In each case the blood pressure evidences of fainting quickly followed.

While, as a rule, warning of the approach of fainting is given in the systolic or diastolic pressure or in the slowing of the pulse rate, there do occur cases in which the observer does not act quickly enough to prevent fainting. In the group studied there were 14 cases of sudden development of the fainting reaction. The data do not give satisfactory evidences of its approach in any case. Usually a fall of 5 mm. or more per minute in the diastolic pressure indicates that fainting is impending, and if to this are added a systolic drop and a slowing of the heart rate the subject must immediately be given fresh air in order to check the process of fainting. Even then the subject sometimes grows worse for a time, but the process is usually completely checked and normal circulatory conditions are rapidly restored. In cases where the rapid diastolic fall appears alone it is ordinarily safe to continue the experiment a minute or two longer until the rate of fall becomes very rapid.

The analysis of the 14 cases, in which the fainting reaction developed unusually quickly, shows how completely a close observer may protect the subject from losing consciousness. Not one of these men actually fainted, in each the process was checked by one or two deep breaths of fresh air. In three of the cases the fall in the systolic pressure had progressed so far that the subject was removed before the diastolic pressure was determined. One case gave the following systolic pressure readings in consecutive minutes: 142, 144, 140 and 80 mm. One minute later, after being taken off, it was 120 mm. In another the pressures the last four minutes were 138, 138, 138 and 68 mm.; beginning two minutes after being taken off they were 104, 114 and 122 mm. In 11 the diastolic pressure was also taken before the subject was restored by fresh air. The rush character of the reaction is quite clear in each. The pressure determinations during the last four consecutive minutes in one case were systolic 134, 136, 134 and 108; diastolic 96, 94, 94 and 64 mm. Another case ran as follows: systolic 124, 120, 122 and 96; diastolic 80, 74, 74 and 46 mm. In this last case the return for the first three minutes after receiving fresh air was as follows: systolic pressure 100, 104 and 108; diastolic 70, 78 and 80 mm. The final oxygen percentages for the group were 10.4, 1 case; 9–9.9, 4 cases; 8–8.9, 5 cases; 7–7.9, 4 cases. The compensatory increase in pulse rate

and respiration was present in all. They did not show a systolic pressure compensation. In five some diastolic compensation occurred.

In the entire experience with more than 7000 rebreathing low oxygen tests, in which the effect of oxygen want was always carried either to demoralization of voluntary attention and motor coördination or until fainting was imminent, there has not been an instance of injury to the subject. There was one man who was allowed to faint, in whom the after-effects persisted for six hours. In no others have there been reasons for worry. Some men, who have been allowed to faint, have felt weak for a while and unusually tired the rest of the day. A frequent after-effect is a frontal headache. While ordinarily it disappears within a few minutes or after getting out into fresh air or in more persistent cases after taking a cup of coffee, in some instances a dull ache has been reported to continue as much as two days.

Comparisons have been made of the curves of reaction of the pulse rate and the arterial pressures for the fainting and non-fainting types with the varieties of curves given in figure 3. The two types are distributed in about equal proportions as regards the variety of pulse rate response. Among the non-fainters there was one man in whom the rate of the heart did not increase, who became mentally inefficient at 10.7 per cent oxygen. Among those of the fainting type there were 5 that gave no pulse rate increase under the low oxygen. They failed at 11.1, 8.9, 8.8, 8.3 and 7.7 per cent of oxygen respectively. Among both types there were some men whose pulse rate increased for a while as the oxygen decreased, but finally ceased accelerating and then maintained a level. Among the non-fainters there were 9 such cases, the plateau began in one at 9.3 per cent of oxygen, in the others later, while in 3 it occurred at less than 7 per cent oxygen. In each case mental inefficiency came on within two or three minutes after the plateau was reached. There were 10 among the fainting type cases whose pulse rate reached a plateau. The earliest to appear was at 12.4 per cent oxygen, while in all it began before 8 per cent was reached. In the fainting type, therefore, the limit of compensation in pulse rate was reached earlier than in the non-fainting type cases.

Approximately 60 per cent of all cases had an initial psychic rise in pulse rate. In one man this amounted to an increase of 43 beats per minute. In the large majority it was less than 15 beats. It ordinarily requires 2 to 4 minutes for this psychic acceleration to disappear. In about 28 per cent of all cases it persists so long that it obscures the beginning of the low oxygen acceleration.

The percentage of oxygen at which the heart rate first begins to accelerate in response to the low oxygen stimulation can not be as accurately determined, in an untrained group of men such as we have here, as it was by Lutz and Schneider (4) in men accustomed to acting as subjects in physiological experiments. We have, however, noted when the acceleration first appeared in 200 of our cases. The results follow:

Between 18–18.9 per cent O_2,	16 cases,	8.0 per cent
Between 17–17.9 per cent O_2,	27 cases,	13.5 per cent
Between 16–16.9 per cent O_2,	29 cases,	14.5 per cent
Between 15–15.9 per cent O_2,	29 cases,	14.5 per cent
Between 14–14.9 per cent O_2,	30 cases,	15.0 per cent
Between 13–13.9 per cent O_2,	28 cases,	14.0 per cent
Between 12–12.9 per cent O_2,	20 cases,	10.0 per cent
Between 11–11.9 per cent O_2,	14 cases,	7.0 per cent
Between 10–10.9 per cent O_2,	6 cases,	3.0 per cent
Between 9– 9.9 per cent O_2,	1 case,	0.5 per cent

The greatest pulse rate acceleration observed during the test among the non-fainters was 57 beats per minute. The mean increase for this type was 27.5 ± 0.6 beats. In the fainting type group the greatest acceleration was 62 beats per minute and the mean increase 26.2 ± 0.6 beats. In this the two types also fail to show a difference.

The systolic pressure responses of the fainting and non-fainting types do not generally follow the same patterns. The non-fainting type cases all gave one or the other of the systolic varieties labeled 2, 2b and 4 (see fig. 3). The terminal compensatory rise in pressure clearly occurred in 93 cases, 58.1 per cent. Men in whom the systolic pressure remained on a level appeared to withstand low oxygen equally as well as those who gave the compensatory rise. The initial psychic rise occurred in 112 cases, 63.8 per cent. It usually was of brief duration, but often persisted for four or five minutes. In a few cases it lasted throughout the test. Some of these will be discussed later. The amount of psychic rise ranged up to as high as 34 mm. The amount and frequency of the rise were as follows: 5 to 9 mm., 11 cases; 10–14 mm., 39 cases; 15–19 mm., 19 cases; 20–24 mm., 28 cases; 25–29 mm., 10 cases; and 30–34 mm., 3 cases.

Among the 139 cases of the fainting type the variety of patterns for the systolic curve was greater, in fact each variety of systolic curve shown in figure 3 occurred. The curves most frequently found were 1 and 5. Of these 79, 57.5 per cent, were variety 1; and 21, 15.1 per cent,

variety 5. Only 35.3 per cent of the cases had the terminal compensatory systolic pressure rise. The initial psychic rise was present in all but 17.3 per cent. The amount and frequency were about the same as in the non-fainting type. In one man this initial rise amounted to 38 mm.

The character of the diastolic changes gave the basis for our subdivision of the two types, so need not be discussed at length here. Varieties 3 and 4 (see fig. 3) are characteristic of the fainting type; although in a few cases, as where the fainting reaction begins with a systolic pressure fall, the diastolic pressure may follow varieties 1 or 2. An initial psychic rise occurred in approximately 55 per cent of all cases. This rise ranged up to 18 mm., but ordinarily was under 8 mm. In about half of all cases in which the rise was present it did not exceed 5 mm.

Respiration. The respiratory reactions of the fainting and non-fainting types have been compared as to the per-minute volume of breathing at the beginning and end of the experiment and as to the

TABLE 5

Respiratory compensation

	VARIETY	NON-FAINTING GROUP		FAINTING GROUP	
		Cases	Percent	Cases	Percent
1	Good compensation with initial psychic	46	29.5	34	26.4
2	Good compensation	84	53.9	51	39.5
3	Slight compensation	20	12.8	29	22.5
4	No compensation	1	0.6	4	3.1
5	Compensation with terminal fall	5	3.2	11	8.5
Total		156	100.0	129	100.0

variety of the curve of reaction. At the beginning the two groups showed approximately the same range, distribution and mean. For the fainting type group this per-minute volume of breathing ranged between 5800 and 16,200 cc., with the mode of the curve at 8000 cc., and the mean 9162±103 cc. For non-fainting type group the range was 4900 to 14,800, the mode 8000 cc. and the mean 9294±90 cc. At the end of the test there was no parallelism. For the fainting type group the per-minute volume of breathing ranged between 7300 and 19,900 cc., with the mean 12,629±144 cc. For the non-fainting group the range was 8200 to 25,000 and the mean 14,406±162 cc. At the end the lung

ventilation of the non-fainting group exceeded that of the fainting group by 1.8 liters. The fainting type had an average increase in the per-minute volume of 3467 cc. while the non-fainting group had 5112 cc. The difference in favor of the non-fainting type explains why this group showed a mean final oxygen of 7.2, while that for the fainting type group was 7.8 per cent; yet it would hardly account for the appearance of the fainting reaction in one and not in the other.

The distribution of the two types with respect to the variety of the curve (see fig. 6) of respiratory reaction was as is shown in table 5. As was to be expected, the non-fainting type followed the good compensation curves in larger numbers than the fainting group.

Early failure. There were 24 out of 300 men who failed to go below 9 per cent of oxygen. Of these only 3 belonged to the non-fainting type. There were 5 men in which there was first a systolic fall, 2 in which there was first a diastolic fall, and 14 in which the systolic and diastolic pressure began to fall at the same time. The clinician's reports of the condition of the subjects prior to the test show nothing abnormal in any case. The men were feeling well, 2 reported a slight cold and 3 a moderate loss of sleep.

The 3 non-fainting type cases were removed by the psychologist for complete inefficiency. One was removed at 10.7 per cent oxygen. His first low oxygen effects on voluntary attention and motor coördination appeared unusually early, at 16.8 and 16 per cent respectively, and there was complete demoralization before he reached 11 per cent. Physiological compensation did not appear until the last minute when the pulse rate increased 6 beats and the respiration, by more rapid breathing, increased 2 liters. The delayed reaction did not revive him mentally. The other 2 men had no respiratory response to the low oxygen and failed at 9.4 and 9.3 per cent of oxygen. One of them showed a good pulse rate reaction in which the acceleration began at 15.5 per cent oxygen and reached a per-minute increase of 20 beats by the end of the test. His per-minute volume of respiration, however, fell off the last seven minutes and was only 7.2 liters the last minute. The rate of breathing was then 15.

Among the 21 men who failed early because of the development of the fainting reaction there were 10 who appeared to be reacting by normal compensation and for whom no explanation of the failure was apparent. Other cases offered possible explanations of early failure. There were 7 who showed early psychological effects; in all but 2 of these the voluntary attention and motor coördination were almost completely

demoralized before the fainting symptoms appeared. Physiologically the 11 men failed to show an increase in the per-minute volume of breathing; one, however, while decreasing the per-minute volume increased the depth of breathing by decreasing the rate. Most of the men showed at least a fair increase in the pulse rate. In one the pulse rate began to accelerate at 17 per cent oxygen and continued to do so to the close of the test at which time it had increased as much as 30 beats per minute. He was a shallow rapid breather, rate 28 per minute, depth 300 cc. Three cases that failed at 11.1, 9.6 and 9.3 per cent of oxygen respectively did not compensate in either the pulse rate or respiration.

The early failures point to respiration as a more important factor than circulation in compensation.

Compensation to 6.9 per cent or less of oxygen. Seventy-one cases of non-fainters who went down to less than 7 per cent of oxygen have been examined to determine the importance of the various compensatory factors. Assuming that the acceleration in the rate of heart beat, the increase in the per-minute volume of breathing, a terminal rise in systolic arterial pressure, and a terminal gradual controlled fall in the diastolic pressure, are compensatory responses to low oxygen, these factors enter into the reaction as follows:

A good response in the 4 factors	24 cases
A good response in 3 factors	30 cases
A good response in 2 factors	14 cases
A good response in only 1 factor	3 cases

An increase of 20 beats in the pulse above the lowest rate observed during rebreathing is considered good, and above 30 very good. A respiratory response in which the increase in the per-minute volume was 5 liters above the lowest volume observed during the early half of the test is considered a good response. A systolic pressure rise of 8 mm. and a gradual diastolic pressure fall of 10 mm. are good averages. There were 7 cases with a pulse rate increase of less than 20 beats; one of these accelerated only 8 beats. In 13 the respiratory response was less than 5 liters, the least was 2.6 liters. In one the diastolic fall was absent, and was less than 10 mm. in 19 more. There was no systolic compensation in 20 and less than 8 mm. in 9 others.

Among the 30 cases with one factor somewhat deficient the pulse rate was slightly below the required amount in 2, both having an acceleration of 18 beats per minute. Respiration was deficient in 4,

in one of which the increase was only 2.6 liters. He, however, breathed less frequently so that the volume of each breath was increased from 750 cc. at the beginning of the test to 1050 cc. during the last two minutes. His heart rate accelerated 34 beats and the arterial pressures showed excellent compensation. In the other cases the deficiency occurred in arterial pressure changes. In 16 of these the respiration increased considerably more than the normal amount, and in 18 the pulse rate increase exceeded 30 beats. By the interplay of the four factors, it appears that these 30 cases are accounted for as to sufficiency in compensation.

The deficiency in compensation for the 14 cases in which two factors are below normal can be explained in all but 4 by extraordinary respiratory and pulse rate increases. In one of the 4 the respiratory increase was only 3.7 liters, but by a slowing in the rate of breathing the tidal volume had just doubled. The pulse rate in this case increased 24 beats, the systolic pressure showed 6 mm. compensatory rise, and the diastolic pressure a gradual fall of 14 mm. Another man who reached 6.7 per cent oxygen had almost no increase in the systolic pressure, a gradual diastolic pressure fall of 10 mm., a pulse rate of 90 that increased to 98 during the last 8 minutes, and a respiratory increase of 4.7 liters, with a proportionate increase in depth. Mentally he held out unusually well. The third man had a gradual terminal rise of 6 mm. in the systolic and a gradual fall of 14 mm. in the diastolic pressure, a pulse acceleration of 30 beats, while his respiration increased only 3.5 liters without a change in the rate but an increase in the depth of breathing. The fourth man failed to have a systolic pressure rise, had very good compensation in diastolic pressure and pulse rate, but only an increase of 4 liters in the respiratory per-minute volume.

The 3 cases below normal in all but one of the compensatory factors showed unusually good (6.5–10 liters) respiratory compensation. Their pulse rates increased 17, 18 and 19 beats respectively. The systolic pressure did not increase; in one the diastolic failed to respond, and in the others fell 8 and 6 mm. respectively. In these 3 the respiratory compensation appears to have spared the other factors.

There was not one of the 71 cases of non-fainters who reached 7 per cent or less of oxygen that failed to make at least a fair amount of compensation in pulse rate or respiration.

There were 18 cases among the fainting type that went down to 7 or less per cent oxygen. Eleven of these showed excellent compensation in all four factors up until the last minute, or two minutes in 2 cases, of the test when the evidence of circulatory collapse appeared.

There were 5 of the 18 men of the fainting type who showed deficient compensation in one of the factors. Of these 2 had no rise in the systolic pressure, but the per-minute volume respiratory increase was unusually high, 6 and 8.2 liters. The other 3 made good compensations in all factors except respiration in which the per-minute volume increase was 2.7, 3.2 and 3.2 liters respectively. The man who gave an increase of only 2.7 liters breathed very deeply for the last four minutes of the test, during the last minute there were 9 breaths of which 5 ranged between 2.5 and 3.7 liters. One of the men, who increased 3.2 liters by a slowing of the rate, more than doubled the depth of breathing; and the other case throughout the entire experiment breathed very deeply, with 11.5 liters per minute at the beginning and much deeper breaths at the end.

There were two men of the fainting type whose compensations were not up to standard in two factors. One of these had a 7.2 liter increase in the total per-minute volume of breathing, but no increase in pulse rate beyond an initial psychic rise at the beginning of the experiment. The pulse rate was 110 beats per minute. The last man showed up well in pulse rate and diastolic pressure compensation, he had an initial psychic rise of 16 mm. in systolic pressure at the beginning, which was maintained without change throughout the rest of the test. His respiratory increase was only 3.2 liters, but the per-minute volume at the start was 11.5 liters and the increase in depth was unusually large, or 240 per cent.

All cases among the fainting type group that reached 7 or less per cent of oxygen appear, therefore, to have made good or excellent compensations as judged by the available criteria.

EVALUATION OF THE SEVERAL COMPENSATORY REACTIONS

While an inspection of many records of rebreathing experiments convinces one that the responses to low oxygen constitute a definite physiological process, yet there are such differences in the degree and pattern of the responses that it is often impossible to determine the relative value of the several reactions. Therefore, a mathematical statement of these relationships has been sought. The coefficient of correlation, which measures the degree of scatter or of concentration of the data, has been determined for the pulse rate increase, the systolic, diastolic and pulse pressure changes, and the respiration increase, with respect to oxygen. For each of these correlations the sign of the coefficient has

been minus and thus has supported the observation that a decrease in oxygen is accompanied by an increase in the physiological response. The degree of correlation between the several compensatory reactions and low oxygen has not been found to be high, but was found to be present in significant degree and in somewhat different measure for each factor. Hence it has been possible to place a value on each response and to arrange them in a scale of importance.

The interpretation of the degree of correlation has been made on the following basis. When the coefficient of correlation was less than -0.15 to -0.20 the correlation has been regarded as negligible or indifferent; when it ranged from -0.20 to -0.35, as present but low; and when it ranged from -0.35 to -0.50 or -0.60, as markedly present (8). In our problem -1 would of course mean a perfect correlation.

TABLE 6

Coefficient of correlation with probable error for physiological responses to low oxygen

PHYSIOLOGIC RESPONSE	NON-FAINTING	FAINTING GROUP
Respiratory increase in deciliters	-0.55 ± 0.04	-0.42 ± 0.05
Pulse rate increase	-0.34 ± 0.05	-0.35 ± 0.05
Systolic pressure rise	-0.40 ± 0.05	-0.43 ± 0.05
Diastolic pressure fall	-0.07 ± 0.05	-0.02 ± 0.06
Pulse pressure increase	-0.29 ± 0.05	-0.43 ± 0.05
Number of cases	160	139
Mean oxygen per cent	$7.2\ \pm0.05$	$7.8\ \pm0.06$

The coefficients of correlation for the physiologic responses to low oxygen have been tabulated in table 6 for our two groups of type cases. The degree of correlation between the several physiological changes and low oxygen agrees quite closely with the results obtained from our study of other selected groups. Assuming, as we believe we are justified in doing from our study of other groups, that the non-fainting group represents the best compensation to low oxygen; then it is clear that the increase in the per-minute volume of breathing is the compensatory factor of first importance. There has been a disposition on the part of clinicians, who have been associated with the Rebreathing Altitude Classification Examination, to consider that the circulatory reactions constitute the only trustworthy criteria of compensatory ability. The relationship established by the statistical analysis places the circulatory adaptive changes in a position of secondary importance. It indi-

cates that a large increase in the breathing is more frequently associated with the toleration of an extremely low oxygen than is a large increase in pulse rate. The coefficient -0.55 for the respiratory increase is fairly high, while -0.34, that for the pulse rate increase, is somewhat low; but correlation is clearly present. That the diastolic pressure change should show an indifferent correlation, -0.07, with the low oxygen was somewhat of a surprise. But as this coefficient of correlation is invariably small in all our groups for which it has been calculated the degree of diastolic pressure fall must, for the present, be regarded as a factor of minor importance. In five groups of cases the correlation of the systolic pressure changes with oxygen has ranged between -0.28 and -0.43, which shows that a part of the compensation to low oxygen is accomplished by a rise in this pressure, and that this factor should be regarded as of at least equal importance with the increase in heart rate. The coefficient of correlation for the pulse pressure change is approximately equal to that of the systolic pressure and has been found to range between -0.26 and -0.44, which would lead us to regard this factor as of more importance than has been our custom.

A comparison of the coefficients of correlation obtained for the non-fainting and fainting types (see table 6) indicates that these two groups differ materially in only two of the factors; that is in respiration and the pulse pressure. A closer study of the correlation computations, however, brings out other differences that will be presented briefly. These differences are found in the arithmetical means and in the standard deviation, which is another measure of the variability that includes the middle two-thirds of all cases.

The mean increase in breathing as determined by the per-minute volume at the end of the test was for the non-fainting type 5120 ± 135 cc., and the standard deviation 2540 cc.; for the fainting type the increase was 3500 ± 127 cc., and the standard deviation 2210 cc. It is clear, therefore, that the per-minute volume of breathing was greater in the non-fainting than in the fainting group.

The mean increase in the pulse rate for the non-fainting group was 28.5 ± 0.6 beats and the standard deviation 11.3 beats; for the fainting group it was 26.2 ± 0.6 beats and the standard deviation 10.3 beats. These differences between the two groups of cases are too slight to be significant.

The systolic pressure changes gave for the non-fainting group a mean rise of 12.7 ± 0.6 mm., with a standard deviation of 11.5 mm., while

for the fainting group there was a mean fall of 1 ± 1 mm., and a standard deviation of 17.7 mm. Hence, although the coefficients of correlation for the relationship between systolic pressure change and low oxygen were approximately equal, -0.40 and -0.43 respectively, yet the non-fainting group had a considerable increase in systolic pressure, while the fainting group on the whole showed very little change.

While the computations do not show the diastolic pressure changes to correlate with the oxygen, yet the two groups gave striking contrast in the arithmetical means and standard deviations. The mean diastolic pressure fall for the non-fainting group was 7.5 ± 0.4 mm., and the standard deviation 6.6 mm.; for the fainting group the mean fall was 18.8 ± 0.6 mm., and standard deviation 11 mm.

The pulse pressure mean increase for the non-fainting group was 23.8 ± 0.6 mm., and the standard deviation 12 mm.; for the fainting group the increase was only 14.2 ± 0.8 mm., and the standard deviation 14.6 mm. These figures point to the systolic pressure changes as more significant in the determination of the final pulse pressure than the diastolic pressure. Just why the coefficient of correlation for the non-fainting group should be less than for the fainting has not as yet been determined.

By this mathematical study it has been demonstrated that, as a rule, men of the non-fainting type increase their breathing more, have a greater rise in systolic pressure, a more moderate fall in the diastolic pressure, and a larger increase in pulse pressure than do the characteristic fainting type reactions.

SUMMARY

A part of the results from a study of 1050 cases of rebreathing has been given. The normal, or usual, responses in respiration, pulse rate and the systolic, diastolic and pulse pressures have been presented by curves. Variations from the normal curve have also been illustrated.

An analysis of 300 cases showed that 140, 46.7 per cent, belonged to the fainting and 160, 53.3 per cent, to the non-fainting type. Each of these types was found to present several varieties that have been briefly considered. Special examinations have been made of cases of early failure and of those who tolerated to less than 7 per cent of oxygen. Computations of the coefficients of correlation and the standard deviation for the relationship between the compensatory factors and low oxygen have shown that the respiration constitutes the primary, and

the circulatory changes the secondary factor in compensation. A large increase in the per-minute volume and depth of breathing, an acceleration in the pulse rate, a considerable rise in the systolic and pulse pressures, and a moderate terminal drop in the diastolic arterial pressure constitute an excellent response to the decrease in oxygen.

The final oxygen percentage for all cases gave an arithmetical mean of 7.42 ± 0.01 with extremes of 11.1 and 5.2. The length of the rebreathing period in which 52 liters of air were used gave for all cases a mean of 24.65 ± 0.05 with extremes of 15 and 37 minutes.

We wish here to express our thanks to Mr. S. Isaacs and Mrs. R. G. Merriman for suggestions and help in handling the statistical data.

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CONTRIBUTIONS TO THE PHYSIOLOGY OF THE STOMACH

LIII. On the Secretory Response of the Gastric Mucous Membrane to Water and Saline Solutions

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Pawlow (1) reported years ago that water is a stimulus to gastric secretion, and that this stimulating action still occurs after cutting the vagi nerves. He also noted that a large amount of water is necessary, and concluded that only prolonged contact of water with the gastric mucous membrane gives constant and positive results. Bergeim, Rehfuss and Hawk (2) demonstrated the direct stimulating action of water on gastric secretion in man. Carlson, Orr and Brinkman (3) suggested three possible factors involved in this stimulating action: *a*, psychic; *b*, more rapid absorption of secretagogues; and *c*, dilution of the blood. They showed that the psychic factor is important in the thirsty animal. The present experiments show that the second and third factors are involved, under certain conditions.

LITERATURE

1. Pawlow (1) states, "The quantity of gastric juice was strikingly dependent upon the amount of water in the organism. . . . If sufficient water be not present, the cells cannot withdraw an adequate quantity for the preparation of the juice. Hence we are able to assist a weakly acting cell, which only abstracts the water with difficulty, by intentionally diluting the blood with an excess of water, which the organism instead of holding back, endeavors on the contrary to expel." (The exact experiments are not referred to here, but the conclusions are probably based on Pawlow's experiments on "sham feeding" in starvation.)

2. Influence of the place of absorption on the degree of stimulation of gastric secretion. Lönnquist (4) showed that water introduced through a gastric fistula, in a dog with the pylorus closed, is in part absorbed

by the stomach. Krschychkowsky (quoted from Babkin (5)) showed that water limited to the fundic portion of the stomach produces no secretion in the Pawlow fundic pouch. On the other hand, Sawitch and Zeliony (6) found that water introduced into the isolated pyloric portion of the stomach caused a secretion in the fundic pouch, but this is especially marked only in case the water is frequently removed and replaced by fresh water. Their figures show a considerable secretion on changing the water every 5 minutes. Lönnquist showed that water introduced into the duodenum with the pylorus closed has a weak stimulating effect. Babkin, reviewing the literature on the subject, concludes that water introduced into the rectum does not stimulate gastric secretion. These experiments show, then, the maximum stimulating effect by water introduced into the pyloric portion of the stomach, a weak effect in the small intestine, and no effect at all if introduced into the rectum. A similar relation is noted regarding the stimulating action of Liebig's extract on gastric secretion. There is no gastric secretion when Liebig's extract is introduced into the isolated fundus (Zeliony, Gross and Krschychkowsky), marked secretion when introduced into the isolated pyloric portion (Sawitch and Zeliony), a less secretion when introduced into the duodenum (Sokolow) than into the stomach, and no secretion at all when introduced into the rectum (Lobassow). Alcohol, which is a stronger gastric stimulant than water, gives similar results except that it also stimulates gastric secretion when introduced into the fundus (Gross) or rectum (Babkin) or directly into the blood (Groeli).

3. Effect on gastric secretion of slowing the emptying time of the stomach. Von Mering (8) found that of 500 cc. of water which the dog drinks, 490 cc. may pass out through a duodenal fistula in 20 minutes. If 250 cc. of milk are introduced into the intestine through the duodenal fistula, and then 500 cc. of water into the stomach, only a few cubic centimeters pass out in the next 30 minutes instead of all the water. Thus the filling of the duodenum slows reflexly the emptying of the stomach. Foster and Lambert (9) showed that the rate per hour as well as the total gastric secretion during the digestion of a meal was increased by experimental pyloric stenosis. In the case of peptonized milk, however, for which the emptying time was not increased by the stenosis, the secretion was not increased. It seems probable that the same mechanism would be effective in the case of water, and that anything which might delay the water in the stomach, such as obstruction of the pylorus, mixture with food, presence of food in the intestine, etc., would increase the secretory response of the stomach to water.

EXPERIMENTAL METHODS

In some of these experiments the attempt was made to eliminate or lessen the error from psychic secretion by using dogs with a Heidenhain pouch, by giving the water through a gastric fistula or by stomach tube. Thus the stimulating action may be assumed to be *a*, by dilution of the blood; *b*, by a more rapid formation or absorption of secretagogues; or *c*, by a possible local nervous reflex.

a. It is well known that the blood becomes measurably diluted after drinking large quantities of water, but whether this dilution of the blood is a stimulus to gastric secretion had never been investigated so far as we know. This was tested by the intravenous injection of water in dogs. The secretion was collected either from an isolated fundic pouch (Pawlow pouch), or from the entire stomach through a gastric fistula.

b. Water absorbed from the alimentary canal involves, in addition to dilution of the blood, a possible stimulating action by means of secretagogues. This was investigated by determining the effect of food in the gastro-intestinal tract on the stimulating action of water. Water was given by stomach tube to dogs with a Heidenhain pouch at various times before, during and after a standard meal. To dogs with Pawlow pouches water was given through an intestinal fistula at different times after the last meal.

Then, eliminating the food factor, direct comparisons were made to determine the relative stimulating effect of water given by stomach tube, by intestinal fistula and by intravenous injection. Rectal injections were also tried. The varying results, depending upon the place of absorption of the water, suggest a gastric secretagogue mechanism as one of the factors.

After it was found that water injected intravenously stimulates gastric secretion, an attempt was made to further analyze the mechanism of this stimulating action by the intravenous injection of salt solutions and salt-gelatin solutions.

As a routine, unless modified for the purpose of the experiment, the animals were used 45 to 48 hours after their last meal and 24 hours after having been given water, in order to have the condition of activity of the gastro-intestinal tract as nearly constant as possible in all the experiments. The starvation period was made this long because in the fistula dogs a few food remnants would occasionally be found in the stomach 24 hours after a meal. All intravenous injections were made

by means of a hypodermic needle without anesthetic, and with no discomfort to the animal. The sterile water or salt solutions were injected at body temperature by gravity, over a period of 5 to 25 minutes.

Each sample of gastric juice was titrated for free and total acidity using dimethylamidoazobenzol and phenolphthalein as indicators. The figures given in the tables are in terms of free acidity calculated as per cent HCl, unless otherwise stated.

RESULTS

I. Intravenous injection of water

1. Heidenhain pouch dog. Water was injected intravenously during the course of the digestion secretion. The "continuous" secretion was collected for 3 to 4 hours after dressing the pouch until the increase in amount, which generally followed changing the dressing, had practically stopped. Then a meal was given consisting of 310 grams of ground fresh round steak from which the fat had been cut. The control experiments summarized in table 1 show the normal secretion of this dog on the standard meal. It will be noted that the amount of secretion from the pouch is small even after feeding, in an animal which has been deprived of water for so long, and that the acidity of the juice seems to be a better criterion of the secretory response than the amount of juice. There was no response (increase over the continuous secretion) during the first hour after the meal, i.e., there is no psychic secretion. The maximum response was reached during the 4th or 5th hour, followed by a gradual decline. If water (19 to 20 cc. per kilo body weight) was injected intravenously as soon as it was certain that the maximum rate of digestion secretion had been passed (expers. 6 and 8), there was a distinct increase during the next half hour, especially in the amount, and also in the acidity of the juice. The maximum response to the injection was passed in half an hour, but the rate of secretion remained higher than the controls for an hour or two longer. Experiments 9 to 12 (table 1) show that the same quantity of water taken into the stomach with the meat meal has a greater stimulating action on gastric secretion than when given intravenously.

In one experiment (data not included here), 28 cc. of water per kilo body weight were injected intravenously in this dog 48 hours after the meal, when the continuous gastric secretion was slow. There followed

increase in the amount of secretion, but no free acid. This small response when the gastric glands were relatively inactive was an indication supported by later observations, that the gastric glands respond to stimulation in proportion to their activity at the time of stimulation.

TABLE 1

Dog (9.5 kilos) with Heidenhain stomach pouch. Influence of intravenous injection of water on the gastric secretion

NUMBER OF EXPERIMENT	EXPERIMENTAL CONDITIONS	GASTRIC SECRETION (AVERAGES)		
		Time	Quantity per hour	Acidity (free) average
		hours	*cc.*	
1–6 (Control)	Continuous secretion	4	2.3	0.00
	After feeding 310 grams lean meat	7	2.3	0.08
7	Continuous secretion	1	3.3	0.00
	After feeding 310 grams lean meat	5	2.6	0.09
	After intravenous injection of 190 cc. water	3	4.8	0.15
8	Continuous secretion	1	4.1	0.00
	After feeding 310 grams lean meat	4	3.4	0.07
	After intravenous injection of 190 cc. water	4	5.2	0.10
9–12	Continuous secretion	4	2.4	0.00
	After feeding 310 grams lean meat with 185 cc. water	7	3.5	0.22

2. Dogs with a simple gastric fistula. Control experiments were run on each dog. A tube was inserted through the fistula and the residuum drained out. In dog 1 there was a fairly high continuous secretion rate, which gradually decreased when the tube was left in situ, and in 3 to 4 hours reached a minimum of from 1 drop to 1 cc. of thick mucus per half-hour. The intravenous injection was made only after the continuous secretion had so decreased that it contained no free acid or gave only a weak acid test with dimethlyamidoazobenzol (expers. 1 and 2, table 2). In 15 to 20 minutes after the intravenous injection, gastric juice began to flow more freely from the fistula, at first with some mucus, later as a clear, watery, strongly acid juice until a maximum rate of 5 cc. per half hour was reached. The secretion period lasted 2 hours in experiment 1 and 3½ hours in experiment 2. The

amount of juice was not large even for a 6 kilo dog, but it was a marked increase over the "continuous" secretion.

In dog 2 (exper. 3), there was a continuous secretion with an acidity of 0.1 to 0.2 per cent HCl. In this experiment also the intravenous injection of water (14 cc. per kilo) caused some increase in gastric secretion, lasting about 1 hour.

The variability of the continuous gastric secretion in dogs with simple gastric fistula is well known to all who have worked with such animals. Possibly there would have been a "spontaneous" secretory

TABLE 2

Influence of intravenous injections of water on the gastric secretion in dogs with gastric fistula

NUMBER OF EXPERIMENT	EXPERIMENTAL CONDITIONS	GASTRIC SECRETION (AVERAGES)		
		Time	Quantity per hour	Acidity (free) average
		hours	*cc.*	
I Dog 1 (6 kilos)	Continuous secretion	4	2.6	Trace
	After intravenous injection of 130 cc. water	2	12.0	0.17
II Dog 1	Continuous secretion	3	2.6	Trace
	After intravenous injection of 143 cc. water	4	14.2	0.26
III Dog 2 (6 kilos)	Continuous secretion	2	3.7	0.18
	After intravenous injection of 85 cc. water	2	5.3	0.20

period at just that time without any water injection, but control experiments on the same dog under the same conditions showed that the low secretion rate continued for 5 to 10 hours without a period of "spontaneous" secretion comparable to that following a water injection. At several times small amounts of water (5 to 50 cc.) were injected intravenously, but in none of these cases was there a secretory response. Thus the stimulation cannot be attributed to any psychic influence connected with the manipulations, and cannot be considered spontaneous. Probably the preceding 24 hour period without water had an important influence in eliminating spontaneous periods of marked gastric secretion.

3. Pawlow pouch dogs (table 3). Experiment shows a definite though small stimulation of gastric secretion by the intravenous injec-

tion of water. The pouch in this dog was unusually small. Experiments 2 to 6 were performed on dog 2. The intravenous injection of 5 cc. of water per kilo body weight (exper. 5) gave a slight response.

TABLE 3

Influence of intravenous injections of water on gastric secretion in dogs with Pawlow pouch stomach

NUMBER OF EXPERIMENT	EXPERIMENTAL CONDITION	GASTRIC SECRETION (AVERAGES)		
		Time	Quantity per hour	Acidity (free)
		hours	*cc.*	
1 Dog 1 (7.2 kilos)	Continuous secretion	1	0.4	0
	After intravenous injection of 144 cc. water	2	1.2	0.025
2 Dog 2 (10 kilos)	Continuous secretion	2	2.0	0
	After intravenous injection of 155 cc. water	2	4.0	0.01
3 Dog 2	Continuous secretion	4	3.5	0
	After intravenous injection of 225 cc. water	4	5.0	0
	After giving 225 cc. water by stomach tube	3	5.3	Trace
4 Dog 2	Continuous secretion	6	2.9	Trace
	After intravenous injection of 150 cc. water	2	4.5	0.015
	After giving 150 cc. water by stomach tube	3	2.7	0
5 Dog 2	Continuous secretion	3	2.1	0
	After intravenous injection of 50 cc. water	2	1.6	0.04
	After giving 50 cc. water by stomach tube	2	0.8	0
6 Dog 2	Continuous secretion	3	2.8	0
	After giving 105 cc. water by stomach tube	3	3.0	0
	After intravenous injection of 105 cc. water	2	3.2	0.01

In another experiment on this same dog, this amount gave no response at all. The response to 10 cc. per kilo (exper. 6) and 15 cc. per kilo (expers. 1 and 2), was more definite and of longer duration. The

injection of 22 cc. per kilo in experiment 3 led to an increase in the amount of juice, but no free acid. This amount caused hemolysis as evidenced by bloody discoloration of the gastric juice and urine.

These experiments show that the intravenous injection of water does stimulate gastric secretion. The response to small injections is not constant. The response to 10 to 20 cc. per kilo body weight is more definite, while larger amounts cause hemolysis.

II. Introduction of water through an intestinal fistula

These experiments (table 4) show a small but definite stimulation of gastric secretion by water introduced directly into the intestine.

TABLE 4

Influence of water on gastric secretion when introduced into the small intestines of dogs with intestinal fistula (also gastric fistula or Pawlow pouch, and pylorectomy or closure of the pylorus)

NUMBER OF EXPERIMENT	EXPERIMENTAL CONDITIONS	GASTRIC SECRETION (AVERAGES)		
		Time	Quantity per hour	Acidity (free)
		hours	*cc.*	
1 Dog 1 (6 kilos) gastric fistula	Continuous secretion	1	1.2	0
	After introduction of 250 cc. water into small intestine	2	4.0	0.11
2 Dog 2 (6.5 kilos) gastric fistula	Continuous secretion	1	3.6	0
	After introduction of 120 cc. water into small intestine	2	10.0	0.08
3 Dog 3 (6 kilos) gastric fistula	Continuous secretion	1	2.6	0.01
	After introduction of 150 cc. water into small intestine	2	4.7	0.14
4 Dog 3	Continuous secretion	2	3.7	0.18
	After introduction of 85 cc. water into small intestine	2	8.8	0.30
5 Dog 4 (5.5 kilos) Pawlow pouch	Continuous secretion	4	0.1	0
	After introduction of 100 cc. water into small intestine	10	2.7	0.12
6 Dog 4	Continuous secretion	4	0.8	Trace
	After introduction of 100 cc. water into small intestine	3	2.0	0.04
	After giving 100 cc. water by stomach tube	2	2.1	0.10

Four dogs were used. In only one dog could the water have passed up through the pylorus into the stomach. The pylorus had been closed by operation in the other dogs. There is a latent period of nearly one-half hour, and the secretion returns to its continuous rate in 2 to 3 hours. This is the typical result when the animal has had no food for at least 45 hours preceding the experiment. In experiment 5, the water was given through the intestinal fistula 22 hours after the last meal. In this case the stimulating effect continued for at least 10 hours. This prolonged action might be due to the presence of secretagogues from food residues in the intestine.

III. Introduction of water into the stomach by stomach tube

1. Heidenhain pouch dog: a. Water given during the digestion of a meal. In experiment 1, 105 cc. of water were given by stomach tube

TABLE 5

Heidenhain pouch dog (9.5 kilos). Influence on gastric secretion of giving water by stomach tube during the gastric digestion of a standard meal

NUMBER OF EXPERIMENT	EXPERIMENTAL CONDITIONS	GASTRIC SECRETION (AVERAGES)		
		Time	Quantity per hour	Acidity (free)
		hours	*cc.*	
1	Continuous secretion	2	2.0	0
	After 310 grams lean meat	5	2.6	0.16
	After 185 cc. water by stomach tube	3	3.3	0.20
2	Continuous secretion	2	1.4	0.05
	After 310 grams lean meat	5	3.2	0.16
	After 485 cc. water by stomach tube	3	4.7	0.26
3	Continuous secretion	2	5.2	0.14
	After giving 185 cc. water (14 hours after standard meal)	4	7.4	0.21
4	Continuous secretion	2	3.9	0
	After giving 550 cc. water by stomach tube	3	4.2	0.02

just after the maximum rate of digestion secretion on the standard meal of 310 grams of lean meat (expers. 1 to 6, table 1) had passed. The rate then increased above the maximum on the meat meal alone. The same amount of water given 14 hours after a meal gave also a marked

response (exper. 3). The same amount 24 hours after a meal gave a slight increase in acidity, from 0 to 0.05 per cent HCl only during the first hour after giving the water. This amount of water 40 hours after the last meal, when the stomach and intestines were probably well emptied of food, gave a slight increase in the amount of juice, but no free acid. Experiment 4, using 550 cc. of water, is the most definite response obtained with water 48 hours after a meal. On the other hand, a smaller amount (405 cc.) given just after the maximum rate of digestion secretion, gave a rate double that reached on the meal alone. Thus a given amount of water has a less and less effect on gastric secretion the longer the time between the meal and the giving of the water. The presence of food in the alimentary canal is an important factor, therefore, in the secretory response of the stomach to water introduced by stomach tube.

b. Water given shortly before or with the meal (table 1, expers. 9 to 12). These experiments are to be compared with 1 to 6 (table 1) which show the secretion of this dog on a standard meal given after 40 hours starvation and 24 hours without water. In experiments 9 to 12 water was left in the cage up to the beginning of the experiment in one case, and in the other case 185 cc. of water were given *a*, thoroughly mixed with the meal, and by stomach tube; *b*, immediately before the meal; and *c*, one-half hour before the meal, respectively. The results of these four experiments are so similar that they are given in the form of a composite. Though under the conditions of these experiments 105 cc. of water without a meal had practically no stimulating action on the pouch secretion in this dog, when it was given with or shortly before the meal, it had a very definite effect in shortening the latent period and increasing the secretory response to the meat.

2. Pawlow pouch dog. Water alone given by stomach tube to a dog with a Pawlow pouch causes a much greater secretory response than to a dog with a Heidenhain pouch, as is the case with other gastric secretory stimulants. In the experiments given in table 6 the water was given 48 hours after the last meal. The water was given repeatedly and was followed each time by a marked secretory response. Apparently there was no fatigue of the secretory mechanism involved. Experiment 1 compared with experiment 2 shows that the response to 200 to 280 cc. of water was of about the same magnitude as the response to a small meal of lean meat.

TABLE 5

Pawlow pouch dog (5.5 kilos). Influence of water given by stomach tube on gastric secretion

NUMBER OF EXPERIMENT	EXPERIMENTAL CONDITIONS	GASTRIC SECRETION (AVERAGES)		
		Time	Quantity per hour	Acidity (free)
		hours	*cc.*	
1	Continuous secretion	1	1.0	0.09
	After 100 cc. water	2	1.3	0.14
	After 200 cc. water	2	6.0	0.34
	After 225 cc. water	2	4.6	0.34
	After 100 cc. water	1	1.6	0.15
	After 225 cc. water	2	4.9	0.31
2	Continuous secretion	2	1.2	0
	After a meal of 50 grams lean meat	4	6.01	0.34

3. Man. The experiments were all done on the same individual in the morning without breakfast, having taken a glass of water at about 11 p.m. the night before. The gastric residuum was removed by means of a Rehfuss stomach tube, and then 500 cc. of water introduced through the tube. At the end of every 15 minutes thereafter for a period of 2 hours, the stomach was emptied as completely as possible. In table 3 the experiments are arranged in the order of the amount of water removed from the stomach at the end of the first 15 minutes. So far as these experiments go, they indicate that the longer the water stays in the stomach, the greater is the secretory response, even though less water is absorbed. Regurgitation of bile into the stomach in the experiments reduced the acidity and increased the amount above that of the gastric secretion. Experiments by Dr. A. C. Ivy in this laboratory on twenty men (10) show that in persons whose stomachs pass the water out quickly, the secretory response to water is less than in persons retaining the water in the stomach for longer periods. These facts confirm Pawlow's finding that long-continued contact of water with the gastric mucous membrane increases the secretory response to water.

Why does longer contact of water with the gastric mucosa increase the secretory response? Water absorbed from the stomach might cause a greater secretory response because there is more gastrin in the mucosa of the stomach and duodenum (11). Experiment 1, table 6, shows that there is little if any fatigue of the secretory mechanism involved in the

water, hence we gave to a six kilo dog a large amount of water (6½ liters of which 2½ liters were given on the last day) but no food for 4 days, and at the end of this period "gastrin" was made from the stomach mucosa, with the idea that if "gastrin" is a part of the physiological mechanism and if the mucosa gastrin can be exhausted by continuous activity, this preparation should be less active than gastrin made from a control dog which had been starved for a similar period, and had received necessary water only through the rectum. Tests of the physiological activity of these two preparations of gastrin on a dog with a Pawlow pouch showed that the control preparation was slightly less

TABLE 7

Man; empty stomach. The gastric residuum removed by the Rehfuss tube and 500 cc. of water introduced. Stomach emptied every 15 minutes thereafter

NUMBER OF EXPERIMENT	TEMPERATURE OF WATER	AT END OF 1ST 15 MINUTES	FOR NEXT 1½ HRS.	ACIDITY (FREE)			BILE
				Low	High	Average	
	°C	cc.	cc.				
1	35	33.5	109	0.02	0.09	0.04	–
2	38	90.0	92	0.01	0.14	0.06	–
3	35	115.0	88	0.02	0.16	0.09	-
4	17	200.0	100	0.08	0.16	0.11	–
5	16	224.0	141	0.06	0.10	0.08	++
6	12	230.0	108	0.04	0.16	0.12	–
7	38	305.0	108	0.01	0.19	0.10	+++

active than that made from the dog which had been given a large amount of water. Continuous gastric secretion induced by water evidently does not diminish the gastrin content of the mucosa.

Carlson has pointed out that digestion of the protein and the gastric mucin of the gastric juice itself by the pepsin-HCl will yield gastric secretagogues similar to those developed in the gastric digestion of protein food. It is obvious that the longer the water is retained in the stomach the more secretagogues from gastric juice autolysis would have time to be formed and pass on with the water into the intestines for absorption.

IV. Direct comparison of the stimulating action of water, given by stomach tube, intestinal fistula and intravenous injection

In experiment 6 (table 4) 100 cc. of water were given through an intestinal fistula, and the same amount later by stomach tube. There was a greater response in the latter case. A comparison of experiments

like no. 1 (table 6) with table 4 shows that the response to water given by stomach tube is considerably greater than to water introduced directly into the intestine.

Experiment 3 (table 2), the injection of 85 cc. of water intravenously, was followed by the introduction of 85 cc. of water through an intestinal fistula (exper. 4, table 6). The secretory activity at the time of giving the water was about the same in the two cases, but the water introduced into the intestine caused a greater secretion of gastric juice.

In experiment 3 (table 3), 225 cc. of water given by stomach tube on starvation caused a little more of a reaction than the same amount by intravenous injection. But when there is food in the stomach (*cf.* the Heidenhain pouch dog), water by stomach tube causes a considerably greater response, especially when considering the free acidity of the juice, than when given intravenously. When using from 5 to 15 cc. of water per kilo body weight, the intravenous injection of the smaller amounts gave a gastric response more constantly, and the larger amounts of water gave a slightly greater response than when the same amounts were given by stomach tube, providing the stomach was empty of food (expers. 4 to 6, table 3). Still larger amounts of water cannot be satisfactorily compared in this way on account of hemolysis after intravenous injection, but there is no doubt 50 cc. per kilo would lead to a much greater response by stomach tube.

In general the stimulating effect of water can be stated thus: Water into stomach > Water into small intestine > Water intravenously.

V. Intravenous injection of salt solutions

Hypotonicity of the blood or dilution of the salts of the blood might be the factor causing gastric secretion when water is injected intravenously. In that case injecting isotonic solutions should induce no gastric secretion. Injections were made of solutions having the proportional quantities of the different salts in Ringer's solution. The standard solution used contained 9.0 grams NaCl, 0.24 gram $CaCl_2$, 0.42 gram KCl, and 0.30 gram $NaHCO_3$ per liter. This solution was used in various dilutions as indicated below. Isotonic NaCl was also injected. All these experiments were performed on dogs with a simple gastric fistula.

Experiment 1 (table 8) shows a marked response after the injection of a 75 per cent standard solution, on what was apparently the end of a rapid secretion period. A similar response occurred with a standard

TABLE 8

Gastric fistula dogs. Influence of intravenous injections of salt solutions on gastric secretion

NUMBER OF EXPERIMENT	EXPERIMENTAL CONDITIONS	GASTRIC SECRETION (AVERAGES)		
		Time	Quantity per hour	Acidity (free)
		hours	*cc.*	
1 Dog 1 (6 kilos)	Continuous secretion	2	2.0	0.27
	After intravenous injection of 136 cc. standard solution diluted one-fourth	2	6.3	0.25
2 Dog 1	Continuous secretion	2	0.6	Trace
	After intravenous injection of 136 cc. of hypertonic Ringer's solution (117 per cent of standard)		4.6	0.22
3 Dog 1	Continuous secretion	2	0.2	0
	After intravenous injection of 136 cc. of hypertonic salt solution 2	2	4.0	0.20
4 Dog 1	Continuous secretion	2	3.4	0.16
	After intravenous injection of 136 cc. hypertonic Ringer's solution (110 per cent of standard)	2	7.1	0.29
5 Dog 2 (9.5 kilos)	Continuous secretion	2	3.0	0.23
	After intravenous injection of 150 cc. 0.88 per cent NaCl solution	2	7.6	0.27
6 Dog 2	Continuous secretion	2	12.0	0.32
	1st hour after intravenous injection of 150 cc. 0.83 per cent NaCl + 0.23 per cent $CaCl_2$	1	8.6	0 (bile)
	Two hour period following	2	16.3	0.29
7 Dog 1	Continuous secretion	2	5.5	0.14
	After intravenous injection of 120 cc. 5 per cent gelatin in standard Ringer's solution	2	15.0	0.23
8 Dog 1	Continuous secretion	2	7.0	0.34
	After intravenous injection of 136 cc. 5 per cent gelatin in standard Ringer's diluted one-half	2	8.0	0.20

solution diluted one-half. More concentrated salt solutions (*hypertonic*) produced a similar response (expers. 2 to 4). NaCl solution 0.88 per cent caused a similar secretory response. When the intravenous injections were made toward the end of a secretion period, as in experiments 1 and 6, the latent period was about 5 minutes instead of 15 to 20 minutes. When the glands are in an actively secreting condition, the latent period is shorter than when they were relatively quiescent.

A solution containing 0.83 per cent NaCl and 0.23 per cent $CaCl_2$ (practically ten times the amount of $CaCl_2$ in Ringer's solution) was injected intravenously in a gastric fistula dog on the down curve of a

TABLE 9

Pawlow pouch dog. Influence of intravenous injection of an excess of calcium on the gastric secretion caused by gastrin

		CONTINUOUS SECRETION (18 MINUTES)	"GASTRIN" SECRETION (15 MINUTE PERIOD)				
Exper. 1	Quantity, cc.	0.6	2.8	2.9	1.4	0.2	0.01
	Acidity (free)	0.14	0.33	0.45	0.40	0.35	
Exper. 2	Quantity, cc.	0.6	3.0*	4.4	3.4	1.5	0.3
	Acidity (free)	0.06	0.11	0.42	0.46	0.40	
Exper. 3	Quantity, cc.	0.3	2.3†	2.3	3.1	0.3	0.2
	Acidity	0	0.21	0.40	0.45	0.36	0.34

* Intravenous injection of 50 cc. standard solution containing an excess of $CaCl_2$.

† Intravenous injection of 125 cc. of standard solution containing an excess of $CaCl_2$.

secretion period (exper. 6). There was a regurgitation of bile almost immediately, and later the secretion became fairly viscous. The acidity dropped more rapidly than usual, and the free acidity remained at zero for half an hour after the end of the injection, but in the next half-hour returned to its former height, beginning another period of rapid secretion. A second trial of two smaller injections of a solution containing an excess of calcium gave similar results, i.e., regurgitation of bile and a rapid decrease in secretion rate, though in these cases the acidity did not drop to zero, and the period of depressed secretion rate lasted for only 10 to 15 minutes.

These experiments on an animal with a simple fistula indicate a temporary inhibition of gastric secretion by the excess calcium but

experiments on a Pawlow dog (table 4) gave contradictory results. In the latter experiments a Ringer's solution, to each liter of which 1 gram of $CaCl_2$ had been added, was injected intravenously during the active secretion period caused by an intramuscular injection of gastrin. The solution used in experiments 2 and 3 (table 9) contained only half as much $CaCl_2$ as that used in experiment 6 (table 8), still the per cent of $CaCl_2$ was five times that of Ringer's solution. The excess of calcium did not inhibit the secretion caused by gastrin.

The gastric secretion following the intravenous injections of water and salt solutions is not due to the decrease in the viscosity of the blood. Experiment 7 (table 8) shows that the response to the injection of a 5 per cent gelatin in the standard Ringer's solution is essentially the same as though the gelatin had not been added. Experiment 8 is similar. The viscosity of the injected solutions was not determined at the time, but determinations on a solution made up in the same way at a later date gave a slightly greater viscosity for 5 per cent gelatin-Ringer's solution as compared with distilled water than the figures usually given for blood.

DISCUSSION

1. Water introduced intravenously: The foregoing experiments show that water injected intravenously stimulates gastric secretion. Water might act then primarily by diluting some one or all of the crystalloids or colloids of the blood. The experiments with the salt-gelatin solutions indicate that the secretion is not due to the dilution of the more common salts of the blood, unless we must assume that Ringer's solution is not an accurate enough substitute for the salts of the blood. Since solutions more concentrated than Ringer's have the same stimulating effect, it is not likely that dilution of salts of the blood is the important factor in the stimulating action of water. The general arterial pressure is hardly affected by such slow injections as were used in these experiments.

Since these experiments do not enable us to state that the dilution of any particular substance or group of substances stimulates gastric secretion, we can only say that the addition of water, Ringer's or physiological saline solutions (isotonic, hypo- and hypertonic) to the blood stream, which may be considered as a dilution of the blood, increases gastric secretion. Perhaps this is not to be considered as "stimulation" in the usual sense of the word. There is a continuous activity of the gastric glands, and the increase in available fluid in the

blood stream makes the extraction of water by the gland cells easier or, in other words, hastens the passage of water and other blood constituents from the blood stream into the secreting cells, and out into the lumen of the stomach, together with the specific elements of the gastric secretion.

Doctor Carlson suggests that the increase in gastric secretion by water and salt solutions added to the blood, directly or indirectly, may be simply an instance of the general tissue reaction of removing the excess fluids from the blood in all cases of hydremia. If this is the correct explanation, transfusion of blood should also augment gastric secretion, and we should expect that water and salt solutions augment the other digestive secretions (saliva, bile, pancreatic juice, intestinal juice) similar to their action on the gastric glands.

2. Water introduced per rectum: If water injected intravenously stimulates gastric secretion, why does not water given per rectum have the same effect? Several experiments were tried to see whether the negative results of previous investigators could be confirmed. It is difficult to introduce a large quantity of water into the rectum and have it remain in the bowel for any length of time. In one experiment, by giving small injections lasting over $2\frac{1}{4}$ hours, about 450 to 500 cc. of water were retained by a Pawlow dog weighing 6.4 kilos, but without any response from the stomach. It is doubtful if the same amount of water given by stomach tube in such successive small injections would cause any considerable stimulation. The negative result may be due in part to the fact that water is not absorbed from the colon and rectum rapidly enough to produce the necessary dilution of the blood. Furthermore, secretagogues for the digestive glands are normally not absorbed from the colon and rectum in important amounts.

3. Water introduced into the small intestine: In the small intestine water may be absorbed rapidly enough to dilute the blood, or it may act directly through hormones in the duodenal mucosa, and it may also act indirectly through its effect on the absorption of secretagogues from the lumen of the tract.

4. Water introduced by stomach tube: On an empty stomach, water given by stomach tube in addition to its action after passing through the pylorus might stimulate gastric secretion *a*, by dilution of the blood; *b*, by a chemical (e.g., gastrin) mechanism acted on by the water directly; or *c*, by facilitating the formation and absorption of secretagogues from food residues and from the auto digestion of the gastric juice itself.

a. Water is probably not absorbed from the stomach rapidly enough to stimulate gastric secretion by dilution of the blood. *b.* The attempt to demonstrate a lessened amount of gastrin in the stomach mucosa after large amounts of water given by stomach tube was negative, but it may be that even if the gastrin is the active hormone substance, it is formed as rapidly as it is used up, or that water is not a strong enough stimulant to lead to its exhaustion. Since alcohol and meat extractives cause a greater gastric secretion when absorbed from the stomach than when absorbed from the intestine, even though they are not absorbed so rapidly, and since the longer water stays in the stomach the greater its stimulating effect on gastric secretion, it seems that the chemical or local nervous mechanisms affecting the gastric secretion in the stomach differ from those acting in the gastric glands via the intestine.

Water given with a meal or during its digestion has a greater stimulating effect on gastric secretion than when given during starvation. This is probably because: *a*, the adding of water to meat hastens, in proportion to the thoroughness with which the water and meat are mixed, the digestion and absorption of proteins. *b*, The mixture of solid material such as food with the water, and the presence of food in the intestine (von Mering), keep the water in the stomach for a longer time, and thus increase the secretory response to the water. The importance of *a* and *b* are much lessened by the passage of water along the canalis gastricus when taken after the food. *c*, The gastric glands when in a state of activity are more irritable. This is shown by the fact that water causes a greater response when injected intravenously if the glands are already active. Furthermore, the latent period after the intravenous injection of a water or salt solution is shorter if the injection is made during active secretion than if made during a period of relative secretory quiescence. This confirms the statement regarding gastric appetite secretion that in "man the latent period depends primarily on the condition of the gastric glands" (Carlson (13), p. 24).

Since an amount of water too small to stimulate secretion by itself will shorten the latent period for a subsequent digestion secretion, it seems probable that in the absence of appetite secretion in man, the drinking of a glass or two of water a half to an hour before or at the beginning of the meal would facilitate the digestion secretion and thus partially compensate for the normal appetite secretion.

CONCLUSIONS

1. The intravenous injection of water and salt solutions (isotonic, hypo- and hypertonic) in dogs increases gastric secretion.

2. Water introduced into the stomach by stomach tube stimulates gastric secretion more than the same amount introduced directly into the small intestine. In general, the longer water remains in the stomach, the greater the secretory response of the stomach to the water.

3. The presence of food in the alimentary canal has a very important effect in increasing the secretory response of the stomach to water introduced by stomach tube or through an intestinal fistula.

4. The gastric glands when in a state of relative activity respond more quickly and completely to a given stimulus than if relatively quiescent.

5. It is suggested that the response of the gastric glands to water and salt solutions introduced intravenously is, mainly, an instance of the general tissue action controlling hydremia (Carlson).

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Studies on the changes in fluid volume under adrenalin, pituiturin, pilocarpine and atropine. F. C. BECHT.

By connecting the subdural space through a wide needle with a Mariotte bottle and a tambour, it was possible without altering the pressure in the fluid system after equilibrium had once been reached, to measure accurately the volume of fluid displaced by the action of those drugs, which ordinarily are supposed to increase the amount of fluid formed. Tracings were reproduced which showed that in the case of adrenalin, pituiturin and pilocarpine, the fluid moves outward into the Mariotte bottle during the pressure phase of arterial and venous pressures only to return to the skull after the blood pressures return to normal. The conclusion was reached that the movement of fluid was due entirely to alteration in blood volume within the skull.

The use of hypertonic salt in experimental increased intracranial pressure. ERNEST SACHS and JULIAN Y. MALONE.

The observations of Weed and McKibben on the effect of hypertonic salt administered intravenously upon brain volume led us to consider using this procedure on patients having increased intracranial pressure due to tumor or due to edema associated with a trauma to the brain. The results were so striking in the few desperate cases tried that it was felt if this method could be shown to have no deleterious effects it would prove a great aid in operative procedures in the intracranial cavity. We therefore carried out experiments on dogs in whom we produced local increased intracranial pressure. Two trephine openings were made, one over each hemisphere. Into one was screwed a metal tube the size of the opening through which passed a tube on the end of which was a rubber bag made of the thinnest rubber dam. This was connected with a pressure bottle and a recording blood pressure manometer was connected with a side tube. With this, local intracranial pressure was produced. The intracranial pressure was kept constant throughout. Into the other trephine opening was fastened a tube over the mouth of which rubber dam was very loosely attached and on this rested a piston attached to a lever to record the brain volume. Brain volume, intracranial pressure, blood pressure and respiration were recorded in all of these experiments. Thirty per cent sodium chloride solution was injected into the femoral vein from a burette.

The points we have studied thus far are:

1. How promptly after the injection is begun does a change in brain volume occur? We have noted a definite change in less than 10 minutes. The maximum shrinkage occurred in from 45 minutes to 1 hour.

2. The effect of the salt lasts for hours but we have not determined when the effect has entirely disappeared. But Foley and Putnam have shown that when hypertonic salt is introduced into the gastro-intestinal tract brain volume changes are still noted 6 to 10 hours later. They however used no graphic method for recording their observations.

3. If the solution is given no faster than 1 cc. per minute there is no change in respiration or blood pressure, and at times 2 cc. per minute may be given without any harmful effect. When the salt is run in too fast the blood pressure drops and the respirations are slowed and become shallower.

4. We have given as much as 9 cc. per kilo body weight in animals without noticeable harm. The rate of administration seems to be the important factor in bringing on toxic effects. In patients we have never given more than 100 cc. of 35 per cent solution.

5. On patients we have never noted any harmful effects on the red corpuscles.

6. We have tried 30 per cent glucose solution but have not obtained any changes. A 30 per cent glucose solution however has only the same osmotic pressure as a 4.5 per cent NaCl solution and to get the same effect with glucose solution would necessitate using a very much more concentrated solution.

We have thus far made no observations to determine whether the change in brain volume is due solely to dehydration, or also affects the change in rate of secretion of cerebro-spinal fluid.

Clinically we have invariably seen a rise of blood pressure after the administration of hypertonic salt both in the unanesthetized and anesthetized patients but we have not observed this in our animal experiments. For this discrepancy we have no explanation.

Based on these experiments we believe that the intravenous injection of hypertonic salt solution is a valuable aid in reducing brain volume in cases of increased intracranial pressure.

A separation of substances eliminated by the kidney into groups on the basis of the effects of changes in blood flow and temporary anemia.
E. K. MARSHALL, JR. and MARIAN M. CRANE.

All experiments have been carried out on dogs under paraldehyde anesthesia. The kidney on one side has been subjected to some experimental procedure and the elimination of this kidney compared with that of the kidney on the normal side. It has been previously demonstrated by Marshall and Kolls (This Journal, 1919, xlix, 302) that the changes occurring after section of the splanchnic nerve can be explained on the basis of an increased blood flow through the kidney. Creatinine and phenolsulphonephthalein were shown to be only slightly if at

all affected by changes in blood flow, while water and chlorides were markedly changed and urea definitely changed but to a less extent than the above.

Additional data have been obtained on other substances, and the following divisions can be made: group 1—water, chloride and carbonate, markedly affected by increased blood flow; group 2—urea, phosphate and sulphate, increased, but to a less extent than group 1; group 3—creatinine, ammonium and sulphonephthalein, not changed by increased blood flow.

Temporary anemia of the kidney has been produced by clamping the renal artery for varying periods of time. Contrary to the opinion universally expressed, a short temporary cessation of the blood flow through the kidney is not followed by a prolonged anuria. In fact, urine secretion is reëstablished in 2 to 3 minutes after an anemia of 20 minutes' duration, and after 1 to 3 minutes anemia no demonstrable changes in the secretion are present except the appearance of protein. If the anemia is of sufficient duration (this varies greatly with individual animal) an examination of the secretion of the kidney after the anemia indicates that substances fall into two sharply defined groups on the basis of the effect of anemia. Group 1 is not affected or may be slightly increased as a result; groups 2 and 3 are more or less reduced in amount. (These groups are the same as for blood flow.) The reduction is by no means the same for all members of either group—ammonium is much more markedly affected than creatinine.

A preliminary examination of the secretion of free and combined carbon dioxide and the primary and secondary phosphates have been made by these methods. The proportion of these has been calculated from the hydrogen-ion concentration. It appears that the two phosphate ions fall into different groups.

The inhibitory influence of the cervical sympathetic nerve upon the sphincter muscle of the iris. DON R. JOSEPH.

The experiments here reported were carried out upon the irises of cats and dogs under ether or ether-morphine anesthesia. The bulbus oculi was fixed by tenaculi so that it was immovable. The cornea was then carefully removed and the intact sphincter grasped by two miniature clamps—one at the inferior pupillary border, and the other at its superior margin. The lower of these two clamps was attached to a rod held rigidly in place and therefore served to fix that portion of the sphincter. The upper clamp was attached to a thread leading to a blue-grass writing lever. Finally the iris was incised in such a way that no radial contractile element of the iris could affect the lever.

The results have been unmistakable. Stimulation of the cervical sympathetic produced a prompt relaxation of the sphincter. The relaxation (inhibition) could be maintained for several seconds by continuation of the stimulation but disappeared after cessation of stimulation, at first fairly rapidly but later more gradually, until the original

length of the muscle was restored. This effect could be obtained repeatedly in the same preparation.

The sphincter muscle of the iris appears therefore to have a double nerve supply; motor, from the third cranial nerve; and inhibitory, from the cervical sympathetic.

Consistency of the protoplasm and character of amoeboid movements. LEO LOEB.

It is generally assumed that amoeboid movements are primarily due to surface tension changes in a liquid medium. In 1901 we found that the pseudopodia of the blood cells of Limulus flow out as a liquid viscid material and then change into a material of the consistency of solid gelatin. It is the shell of the outflowing mass which hardens. These and other observations suggested to us that amoeboid movement is primarily due to alternating and reversible changes in the consistency of the protoplasm, to which in certain cases are added changes in surface tension.

Recently we made additional observations which can be best explained by assuming primary changes in consistency of part of the protoplasm as the determining factor in amoeboid movement. We found that we can experimentally modify in every possible way the character of the amoeboid movement by changing the medium in which the cells move. We make use of the experimental cell fibrin tissue from which the cells migrate into the surrounding fluid. By modifying the osmotic pressure, using graded solutions of NaCl, all kinds of pseudopodia can be produced, large branching threadlike formations in hypertonic and large balloons and other formations in certain hypotonic solutions in addition to the normal tonguelike pseudopods. The granuloplasm moves into these extreme pseudopods as it does into intermediate ones, which develop in isotonic solutions, but with a velocity which varies in accordance with the consistency of the protoplasm. In slightly hypotonic solutions of KCl the consistency of the granuloplasm is changed in addition and circus movements result.

Gradually the blood cells spread out in contact with solid bodies. In doing so they send out long pseudopods which in their outer shell become solid and connect the different cells. This tissue resembles morphologically connective tissue. Gradually this tissue retracts in a way similar to connective tissue and fibrin. This is due to the elasticity acquired by the hardened cell material. This suggests the possibility that changes in elasticity of the cell exoplasm after it has hardened may play a part in the amoeboid movement.

On the basis of our observations we may conclude that the formation of drops on the surface of the cell during cytolysis and the formation of a fertilization membrane are phenomena related to the formation of pseudopods, the former representing extreme conditions which when of an intermediate degree lead to normal pseudopodial activity. Experimentally all possible transitions can be produced between these formations.

Thyro-parathyroidectomy in the sheep.[1] SUTHERLAND SIMPSON.

In November and December, 1919, the thyroid gland (including the internal parathyroids) and two external parathyroids were removed from four adult ewes—5 years or over—, the thyroid, with internal parathyroids from a fifth, while a sixth, uninjured, was kept as a control. All the ewes turned out to be pregnant, although this was not known at the time.

Of the four which were subjected to the complete operation, none showed any acute symptoms but in about 9 weeks two of them began to lose weight and to fall off in appearance. One died on March 3, 1920, and at the post mortem two dead fetuses were found in utero. The second dropped a dead fetus on April 2, and after this improved somewhat but on May 22 symptoms of tetany were observed. On May 25 these became acute, and after a record had been obtained, the animal was killed by chloroform.

The remaining two showed no symptoms at any time One dropped two healthy lambs on April 15, and the other one lamb on April 16. The ewes were slaughtered on December 11 and 16, respectively, and a very careful search made for accessory thyroid and parathyroid tissue. In the one which had dropped and suckled two lambs five suspicious pieces of tissue were removed from the neck; on microscopic examination, three of these proved to be hemolymph nodes, and two, measuring $5 \times 3 \times 2$ mm. and $7 \times 5 \times 4$ mm. respectively, consisted of thyroid tissue. No accessory parathyroids were found. In the other which gave birth to one healthy lamb, one piece of thyroid was found—$11 \times 6 \times 4$ mm. and imbedded in the submaxillary gland, a small nodule, $2 \times 3 \times 3$ mm., which showed the structure of parathyroid, together with a considerable quantity of lymphoid tissue.

The fifth sheep, with the two external parathyroids left intact, died on April 12 of "acute exudative rhinitis and pneumonia," as reported by Doctor Goldberg of the Veterinary College, who made the post-mortem examination. One full-term fetus was found in utero. This animal had continued to gain in weight up till the time of death.

The control dropped one healthy lamb and remained normal.

The chief point of interest is that no manifestations of acute tetany were observed, even in the pregnant state, to follow removal of the parathyroids, except in one case and that months after the operation and weeks after abortion had taken place.

Ammonia production in the nerve during excitation. SHIRO TASHIRO.

During the passage of the nerve impulse, the nerve fiber gives off another substance besides carbon dioxide. This substance is volatile and basic in nature. This volatile base forms a soluble yellow color with iodide complex of mercury (Nessler), and gives insoluble white precipitate with Na_2HgCl_4 in alkaline solution (Grave). It is most probably ammonia, although the possibility of being one of the low

[1] The expenses of this investigation were defrayed by the Sarah Manning Sage Fund for Research in Medicine at Ithaca, N. Y.

class of volatile amines is not entirely eliminated. The quantities of this substance were estimated as ammonia. This ammonia production in the nerve is variable under different physiological conditions. Fresh resting nerve gives off some; stimulation increases it. On standing the amount gradually falls off—the fact suggesting that this ammonia formation is not due to similar decomposition of urea in the muscle which Gad-Anderson discovered. The increased amount of ammonia in the nerve during stimulation is almost great enough to neutralize the increased CO_2 production during stimulation. The physiological and biochemical significance of ammonia production in this tissue has not yet been investigated. The fact that the muscle gives off far less ammonia than the nerve is rather significant because the muscle is very sensitive to minute amounts of ammonia, while the nerve is relatively immune to it. The apparent lack of measurable fatigue in the nerve during continued excitation may have a certain relation to the formation of ammonia which tends to neutralize the increased CO_2 production on excitation.

Vagal apnea. WALTER J. MEEK.

In recent years the emphasis has been so strongly laid on the gaseous content of the blood and its influence on the respiratory center that the existence of any other form than chemical apnea has been pretty generally denied. That there is a true chemical apnea one would scarcely think of doubting after the crossed-circulation experiments of Fredericq, but this brilliant demonstration by no means necessarily excludes the possibility that sensory inhibitory impulses reaching the respiratory center during inspiration may not be summated, thereby producing the so-called "vagal apnea."

Two sets of experiments have been carried out in order to obtain light on this point. In dogs under ether anesthesia it was first demonstrated that a given number of inflations would produce an apnea. Both vagi were then cut and it was usually found that the same number of blasts no longer produced apnea. Electrodes were then placed under the central end of one vagus and simultaneous with each blast a weak tetanic stimulus was sent into the nerve. The result was an apnea equal in length to the original.

The second set of experiments consisted in inflating with various strengths of carbon dioxide, on the assumption that if an apnea could be produced with a concentration of CO_2 equal to or greater than that in alveolar air, it would be evidence of some origin not chemical. In this we have succeeded. In one case an apnea almost equaling that obtained with air was secured with an atmosphere containing 10.1 per cent of carbon dioxide. Short periods of apnea have been repeatedly obtained with 6 to 7 per cent CO_2.

These results have led us to conclude that there is a nervous factor in apnea and that at times this may of itself be effective. Although it would seem that the vagi were the chief pathways for these impulses, it is of course possible that other sensory nerves may also have functioned.

Studies on the physiological effects of x-rays: 1, On the variation in the lethal dose during metamorphoses in the fruit-fly, Drosophila. JAMES W. MAVOR.

Accurately determined doses of x-rays were given to pupae of Drosophila at various times after the beginning of pupation. The lethal effect was determined both by counting the number of pupae from which imagoes emerged and by recording the length of life of emerged flies. The results of both series of observations show that there is a definite period in pupation lasting from 12 to 18 hours during which the resistance of the pupa of Drosophila to x-rays increases tenfold.

Movements of the empty stomach of Necturus. T. L. PATTERSON.

The studies were made on Necturus maculatus by the balloon method, the balloon being introduced through an esophageal fistula on the lateral surface of the body just posterior to the forelimb. The contractions are practically continuous like those of the bullfrog but the type and rate resemble more those of the turtle. In prolonged fasting there is a tendency for the contractions to increase in vigor in a manner similar to that found in the turtle. Weak acid or alkali of the usual strength when introduced directly into the stomach, or irritation of the gills, produces temporary inhibition of the movements of the empty stomach.

Readjustment of the peripheral lung motor mechanism after bilateral vagotomy. T. L. PATTERSON.

Carlson and Luckhardt have shown in acute experiments (1 to 2 hours) that destruction of the medulla or section of the vagi in the frog leads immediately to a permanent hypertonus or incomplete tetanus of the lung neuro-muscular mechanism which makes the lung practically non-functional as a respiratory organ. This investigation was to determine whether this hypertonic condition was permanent or temporary. The method consisted of sectioning the vagi in the neck of the frog (Rana pipiens) and after recovery making direct observations on the living animal. Animals in which bilateral vagotomy has occurred lose their normal body contour and the body line becomes straight and may even curve in. This is due to the marked hypertonic condition of the lungs since the nerve section destroys the peripheral lung automatism. The buccal or passive movements are little affected but there is absence of the quick respiratory movements of the lung. In unilateral section of the vagus there is loss of lung automatism on the side of the section only. In both unilateral and bilateral section of the vagi there is a gradual physiological readjustment of the peripheral lung motor mechanism which usually starts from 12 to 21 days after the nerve section when the lung begins to slowly distend and the true lung respiratory movements which at first are very feeble gradually increase to about normal. This recovery is only partial and although the lung again becomes functional through its readjustment, this is not complete at least for a period up to 4½ months after the nerve section. It is evident, therefore, that if the animals are well tended and fed they will live indefinitely after bilateral vagotomy. The autopsy findings are in accord with the above results.

A study of denervated tissue. F. A. HARTMAN and W. E. BLATZ.

The sciatic or tibial nerve was cut or crushed in both limbs of more than 200 rabbits. In 125 of these the severed nerves were separated so as to check regeneration for periods of time ranging from 1 to 7 months. At the end of this period the two ends were freshened and brought together by suture.

The power of the gastrocnemii groups to respond to supermaximal stimulation was tested within 1 or 2 days following the primary operation and at intervals of 10 to 12 days during the remainder of the experiment. This was done while the animal was anesthetized with ether. The amount of work calculated at the optimum load was used as a basis of comparison for the functional capacity of the muscles.

The denervated muscles on the right side were either massaged or treated with galvanic stimulation daily.

Animals have been studied in this manner for periods as long as one year following the primary operation.

Neither massage nor galvanic stimulation prevented the loss in galvanic response which normally develops a few days after denervation. Treatment likewise did not appear to cause a more rapid recovery of the muscle when the nerves were permitted to grow down to the muscle fibers.

Galvanic response and voluntary function in the denervated muscle returned much earlier in crushed nerve cases than in cut and sutured cases.

In all of our work we have been unable to demonstrate benefit from massage or galvanic stimulation.

Fatigue in frog muscle when immersed in various concentrations of lipoid-solvents; especially the higher alcohols. F. M. BALDWIN.

Making use of a proper laboratory apparatus herein described in which experimental conditions may be kept reasonably constant, records were obtained in the development of fatigue in the gastrocnemius muscle of the frog while being subjected during its stimulation to certain computed concentrations of various alcohols.

The ranges of concentrations explored may be briefly tabulated; strong and saturated solutions of methyl, ethyl, propyl, butyl, amyl, heptyl, octyl and capryl, with computed gradations in three series of each, varying from 29.1 methyl, to 0.62 vol. per cent octyl; 20.8 vol. methyl, to 0.29 vol. per cent octyl; and 12.4 methyl, to 0.15 vol. per cent octyl, respectively.

On comparative analysis of the various phases of these curves certain inferences can be drawn as to penetration and its resulting effects on the muscle of the different alcoholic concentrations used, both as to stimulation or sensitization and inhibition or anesthetic effects. Strong concentrations in general give remarkably uniform modifications in phases of contraction, especially in producing immediate contracture which merges without interruption into irreversible secondary contracture. Certain weak solutions are markedly stimulating as evidenced

by initial and somewhat prolonged relaxation phase followed by a reversible contracture phase which is very pronounced. Certain predictable differences were obtained in concentrations between the two extremes.

The evidence presented would seem to indicate that muscles when undergoing the process of fatigue are qualitatively susceptible to differences in concentration of the medium with which they are surrounded. This implies that an intimate relation exists between the physical state of the muscular envelope (plasma-membrane) and the changing physiological conditions within.

Studies in the physiology of the liver. I. Technic and general effects of removal. F. C. MANN.

A method is described for the total removal of the liver of the dog without complicating factors other than the anesthetic. The method consists in performing a three-stage operation. In the first stage a reverse Eck fistula is made, uniting the portal vein and vena cava and ligating the vena cava between the entrance of the right lumbo-adrenal vein and the hepatic veins. A few weeks later at a second operation the portal vein is ligated. At a third operation at a later period total extirpation of the liver is performed. This makes it possible to study the effect resulting solely from the loss of liver tissue. An animal from which the liver is removed by this technic recovers from the immediate effects of the operation and then presents a definite and characteristic syndrome, a sequence of events invariably ending in death.

The length of life following total removal of the liver during which the animal seems normal, usually varies from 5 to 8 hours. The animal then develops muscular weakness, becomes perfectly flaccid and comatose, then fine muscular twitchings appear which increase in severity until definite convulsions occur, during one of which the animal dies.

II. The liver as a regulator of the glucose concentration of the blood. F. C. MANN and T. B. MAGATH.

Following total extirpation of the liver in dogs, there is a progressive fall of blood sugar. Coincident with this fall of blood sugar, there is a decrease in the glycogen content of the muscle. The first symptoms noted after the removal of the liver occur coördinately with this decrease in blood sugar. For instance, the animal appears perfectly normal in most cases until the blood sugar reaches 0.06 per cent when the first signs of muscular weakness are noted. By the time the animal is perfectly flaccid and comatose, the blood sugar has dropped to 0.05 per cent or 0.04, and at the time of death, it is 0.04 per cent or 0.03. If, during any stage after the development of symptoms, up to the point at which respiration has actually stopped, glucose is injected, the animal immediately and completely recovers. The time that the animal appears to stay normal depends on the amount of glucose

injected. Then the same set of symptoms develops and the animal again becomes moribund. Injection of glucose will again restore the animal to a normal condition. This process can be repeated many times. After 15 to 30 hours another set of symptoms develops and the animal may die with the blood sugar not below normal. If the glucose is administered orally or by rectum, the blood sugar may not decrease, in which case the first set of symptoms does not develop. No other substance has been found which will produce this restoration, except maltose and galactose.

The effect of the removal of the liver in geese is just the same as that occurring in dogs, except that the symptoms are not so marked; blood sugar does not drop so low, although the percentage drop is as great, and the restoration after the injection of glucose is not maintained for so long a time.

It would seem from this data that it is of vital necessity that a certain minimum percentage of glucose be maintained in the blood. This low limit of glucose concentration probably is not absolute but may depend on difference in species, difference in individuals and a difference in whether the reduction is slow or fast. This level, however, seems to be controlled by the liver and in this respect the regulation of blood sugar by the liver is an absolutely vital function. The cause of death following removal of the liver in which the blood sugar is kept within the normal limits by the intravenous injection or its administration orally or by rectum, has not yet been determined.

If the pancreas has been removed previous to the removal of the liver the decrease in blood sugar occurs seemingly more quickly than in animals in which only the liver has been removed. At least a larger amount of sugar leaves the circulation as such. It has also been noted that, at least in geese, the injection of glucose following development of symptoms in which both pancreas and liver have been removed has the same effect as in the fowls in which only the liver has been taken out. These data can be interpreted in different ways. It is tentatively suggested that the removal of the pancreas does not prevent the tissues from using glucose but does prevent them from using it efficiently. Since the glucose is only partially used the intermediate products are immediately built up by the liver into glucose.

III. The nitrogen constituents of the blood following removal of the liver. F. C. Mann and T. B. Magath.

Following total removal of the liver there is a fall in blood urea in dogs, often being reduced more than 50 per cent. In geese there is a rapid rise in blood urea following extirpation.

While a normal dog has no uric acid in his blood, there is present following total removal of the liver a rather large amount, increasing the longer the animal lives. In geese there is a marked fall in uric acid. It would appear that either the liver controlled the metabolism of purines to a large extent, or that this is an expression of lowered oxidation.

The ammonia excretion in the urine is greatly increased, perhaps chiefly at the expense of urea, and the ratio may finally reach a level of 1:2. At this stage "rest nitrogen" increases rapidly in both blood and urine. There is, however, no great change in pH or CO_2 combining power of the blood.

Creatinine in the blood does not change following liver extirpation.

Blood non-protein nitrogen increases as does blood amino acid nitrogen. Injection of glycocoll is followed by a rapid, almost quantitative, increase in blood amino nitrogen, and after 5 hours both non-protein and amino acid nitrogen are elevated to a point only slightly lower than maximal.

It would appear that the liver is a very important organ in nitrogen metabolism.

The changes in hydrogen-ion concentration coincident with the growth of Bacterium tumefaciens and other plant pathogens. WILLIAM H. CHAMBERS.

Bacterium tumefaciens, which produces intumescence in infected plants, is compared in bouillon culture with Bacillus solanacearum and Bacterium campestris, which dissolve the plant tissue. The growth curves of the three organisms are similar. Daily determinations of changes in hydrogen-ion concentration show a greater alkali production by Bacterium tumefaciens. This calls attention to the reported alkaline increase in plant tumor tissue over normal tissue.

Variations in the hydrogen-ion concentration of the sweat, sensible, regional and tota[1]. G. A. TALBERT.

When parts of the body are enclosed in rubber jackets, the total sweat thereby invariably shows higher hydrogen-ion concentration then when compared with the sensible sweat. This is especially manifested when comparing the secretion of the enclosed leg with that of the bare leg taken simultaneously. Likewise the simultaneous secretions from different parts of the body show a striking variation; that from the leg is always higher in acidity than from the trunk or arms. The last two run fairly close. Carbon dioxide seems to be a negligible factor.

Plasma chlorids and edema in diabetes.[1] RUSSELL M. WILDER and CAROL BEELER.

A common occurrence n diabetes is an absolute lowering of the chlorid content of the blood plasma. Values as low as 4.8 gm. per liter are at times observed. Of more frequent occurrence is a relative reduction, that is, plasma chlorids low in relation to the accompanying rate of urinary chlorid excretion, or a low renal threshold for chlorids. McLean and Fitz have noted such low thresholds in a majority of observations made on diabetic persons.

[1] This report is published in full in The collected papers of the Mayo Clinic, 1920, xii.

In the course of a series of chlorid threshold determinations in cases of diabetes of varying severity we have observed that the presence or absence of depression of the threshold and its degree depend on the degree of inanition of the patient. A low threshold has always been found in cases of much weight loss, except in cases in which the diabetes has been complicated by nephritis. McLean's studies revealed a tendency to elevation of the threshold in nephritis, and this apparently holds good even in the presence of diabetes. We have further noted that the patients with the lowest absolute plasma chlorid values and the most marked lowering of the chlorid threshold were those manifesting the well-known peculiar edema of diabetes and that the disappearance of such an edema, under dietetic or medicinal treatment, was accompanied by the elevation of the threshold to normal or nearly normal values.

The characteristic diabetic edema occurs mainly in patients who have become cachectic, as was noted by Naunyn. It is not usually accompanied by albuminuria or other evidence of disease of the heart or kidneys. In our observations dilatation of the heart, cyanosis, dyspnea and pulmonary or hepatic congestion have been absent, albuminuria lacking, and renal function, measured by the excretion of nitrogen or the phenolsulphonephthalein test, usually normal. No oliguria accompanies the formation of the edema, this depending more on increased intake of water than on the suppression of urine. Likewise no very marked suppression of salt excretion is evident; a large daily excretion of sodium chlorid accompanies the maximal edema. The feeding of sodium chlorid, as has long been known, favors the formation of the edema, but a rising edema occurs at times with a normal salt intake. Excessive salt feeding, 15 gm. or more daily, is accompanied by accelerated elimination so that while the absolute plasma chlorid value may rise as a result, the chlorid threshold actually falls. Many of these phenomena are in striking contrast to conditions existing in cardiac or nephritic edemas.

Both the edema and the behavior of the chlorid threshold are independent of the state of the acid base equilibrium of the body, as measured either by the carbon dioxid capacity of the plasma or by the titratable acid or ammonia excretion of the urine. Increasing edema and lowering chlorid threshold may accompany diminishing acidosis, and vice versa. They are likewise independent of the degree of glycemia and of the presence or absence of glycosuria.

Edema in diabetes differs fundamentally therefore from the edemas in diseases of the heart and kidneys. The determining factor seems to be inanition which relates it to the hunger edema of war times and other edematous conditions of undernutrition.

Oxygen consumption during repeated slight hemorrhages. H. H. Schlomovitz, Ethel Ronzone and Benj. H. Schlomovitz.

The oxygen absorption in dogs before, during and after $\frac{1}{8}$ to $\frac{1}{3}$ of 1 per cent of the body weight in blood was removed at intervals so that

30 to 40 per cent of the total blood volume was taken in an average of 2 to 3 hours. Under ether anesthesia tracheotomy was performed, a carotid blood pressure cannula inserted, femoral artery and vein exposed. The trachea was connected with a metal oxygen container which recorded the rate and depth of respirations as well as the amount of oxygen absorbed. The CO_2 was absorbed by NaOH solution. Two series of experiments, one with ether inhalation and one with intravenous paraldehyde anesthesia were done, each series respectively divided into controls and bleeding experiments.

The figures of oxygen absorbed in cubic centimeter per square meter body surface in the controls under ether anesthesia compare favorably with determination of other workers on dogs at rest. The bleeding experiments show that there seems to be no marked decrease in oxygen consumption until bleedings of about 1.5 to 2.5 per cent of the body weight or 15 to 25 per cent of the blood have been done. It has been shown by other workers more recently, Eyster and Meek, that it is at this stage that a circulatory and respiratory crisis occurs. It is conceivable that an anoxemia is reflected by the reduced oxygen consumption, increased respiratory rate, reduced alkaline reserve, hyperglycemia, etc. Decreased cardiac output and decreased oxygen-carrying capacity of the blood both lead to decreased oxygenation of the tissues.

The rate of methemoglobin formation from carboxyhemoglobin. THEO. K. KRUSE.

Human blood was hemolyzed by dilution in water, 1 in 100. This solution was divided into two parts, one of which was saturated with oxygen and the other with carbon monoxide. Both solutions were treated with dilute potassium ferricyanide for determination of the rate of methemoglobin formation by spectroscopic and colorimetric methods. The end point in the former method is the complete disappearance of both the oxy and carboxyhemoglobin spectrum. The end point of the latter, under the conditions studied, is a light yellow color. The color of an incomplete reaction ranges from a red to an orange brown. The influence of temperature, concentration of reagent, concentration and freshness of hemoglobin were found to be factors affecting the rate of reaction.

It was found that the rate of methomoglobin formation from carboxyhemoglobin is 160 to 200 times slower than it is from oxyhemoglobin.

This observation explains why blood containing carbon monoxide, with potassium ferricyanide treatment liberates its gas more slowly than when it is absent, for the gases combined with hemoglobin are not fully liberated until the methemoglobin reaction is complete. This delay of carbon monoxide liberation was previously incorrectly associated with an hemolysis factor.

A method was described in which the difference of the rate of methemoglobin formation is utilized as a qualitative and approximate quantitative method for carbon monoxide in blood.

Salt antagonism in Artemia. E. G. MARTIN and BLAKE C. WILBUR.

Artemia salina franciscana (Kellogg) occurs in brine pools. If salinity of sea-water is given value of 1, brines in which the specimens studied in this investigation were found ranged from a salinity of 2.5 to 10 (saturation).

Adult size varies conversely with salinity of brine. Fully developed, large-size adults were found in brines of salinities 2.5 to 5. Largest females weighed 35 to 38 mgm. In strong brines (salinities ranging from 6.5 to 10) largest specimens found weighed 1.8 mgm.

It is stated (Thompson on *Growth*) that body-fluids in Artemia have a normal salt-content below that of sea-water, and much under that of the brine in which they live. We confirm this finding. A distilled water extract yielded 0.006 gm. ash the gram shrimps. Assuming one-half the weight of the shrimps to be fluid this gives a salt content slightly under one-half that of sea-water.

Salt equilibrium is maintained at outer body-surfaces rather than at cell-surfaces. Outer body-surfaces must be highly resistant to inward diffusion of salts, and also to outward movement of water by osmosis. Marked impermeability in strong brine may explain failure to grow.

Transfer of shrimps from natural habitat to a less favorable environment brings about a decline in rhythmic activity, resulting ultimately in complete immobility, even to artificial stimulation. Unfavorable environment induces breakdown in resistance at body surface.

Adult shrimps endure transfer to weaker brine, or even to sea-water, but only immature shrimps survive transfer to a stronger brine than that to which they are habituated.

Average duration of mobility of shrimps transferred to distilled water was 30 ± 0.7 hours (24 experiments, 10 shrimps in each experiment). This was the case regardless of the strength of the brine from which the shrimps were transferred.

Average mobility in unmixed solutions was as follows:

Sodium chloride:
0.5–1.0 mol., 125 hrs.; 1.25–2.75 mol., 67 hrs.; 3–5 mol., 18 hrs.
Potassium chloride:
0.0025–0.025 mol., 12 hrs.; 0.03–0.5 mol., 6 hrs.
Calcium chloride:
0.01–0.09 mol., 28 hrs.; 0.1–0.5 mol., 12 hrs.
Magnesium chloride:
0.1–1.0 mol., 28 hrs.; 2.0–4.0 mol., 9 hrs.

Mixtures of above four salts tested in various proportions. No mixture lacking sodium chloride gave mobility greater than that regularly seen in distilled water.

Inclusion of sodium chloride in mixture regularly gave mobility exceeding that in distilled water, but only exceptionally mobility greater than in pure dilute sodium chloride solution.

In two experiments, one with mol. sodium chloride plus 0.2 mol. magnesium chloride; the other with 1.38 mol. sodium chloride plus

0.162 mol. magnesium chloride plus 0.03 mol. calcium chloride, mobility persisted more than 300 hours on the average. No other mixtures gave better results than pure sodium chloride solution.

Highly concentrated mixtures invariably resulted in loss of mobility within 20 hours, regardless of their constitution.

Hydrochloric and sulphuric acids, in dilutions between 0.001 and 0.1 mol., abolished mobility within one-half hour on the average. The addition of sodium or calcium chloride to the solutions did not prolong mobility.

Return of immobile shrimps to brine from which they were taken originally resulted frequently in restoration of mobility. In many cases, notably after distilled water, potassium chloride solution, and dilute sodium chloride solution, return of mobility occurred within 10 minutes after transfer to brine, suggesting that the immobility was an inhibition rather than the result of a profound change in the salt equilibrium in the cells.

No clear cases of returning mobility were seen following transfer to other solutions than original brine, except that a more dilute brine than that from which the shrimps were originally taken sufficed in some instances to restore mobility.

Prolonged immersion in the solution which abolished mobility prevented its return upon transfer to brine. About half of all shrimps transferred to brine after comparatively short immersion in immobilizing solutions recovered mobility. Various immobilizing solutions were about equal in this respect, except that strong sodium chloride solution appeared least favorable to subsequent recovery.

Studies in the physiology of the circulation. V. Second wind. R. G. PEARCE.

Experiments were conducted on five men in order to determine what change occurs in the respiration, circulation and oxygen consumption during "second wind."

In those who developed second wind we found the volume of the respiration decreased, the percentage of carbon dioxide in the alveolar air increased, and the tension of carbon dioxide in the blood returning to the lungs decreased after the onset of "second wind." The oxygen consumption per minute was not decreased during second wind in our experiments. Unfortunately the exercise chosen for our experiments was too severe to maintain sufficiently long to settle this latter point.

The experiments indicate that during second wind the minute volume of the circulation is greater in proportion to the oxygen consumption than it is before the onset.

The response of a muscle to submaximal stimulation of its motor nerve as affected by reflex excitation and inhibition. L. R. WHITAKER and A. FORBES.

Verworn established the fact that reflex inhibition of skeletal muscle is central and not peripheral by showing that a muscle gives as large a

contraction in response to stimulation through its motor nerve while the motor neurons are being inhibited as when they are not. Forbes and Rappleye[1] found reason to conclude that during voluntary contraction of skeletal muscle the nerve impulses follow each other in the motor neurons at such frequency that each occurs during the relative refractory period following its predecessor; that is, with a rhythm of at least 300 a second and probably much more. If this conclusion and the analysis of nerve and muscle rhythms with which it was reinforced are correct, and if the sustained contractions of extensor muscles involved in decerebrate rigidity, in the crossed extension reflex, and in the extensor rebound following inhibition, are of the same nature as voluntary contractions in the matter of nerve and muscle rhythms, then the response of an extensor muscle to stimulation of its motor nerve should be greater during reflex inhibition than during any of these forms of reflex excitation. The reason for this is that those nerve fibers which conduct impulses with such rapid rhythm are always either absolutely or relatively refractory. During reflex inhibition, if it be complete, no fibers are active and therefore all are excitable. Therefore, a larger percentage of motor nerve fibers will respond to a stimulus of a given strength during inhibition, and a correspondingly larger percentage of muscle fibers will be made to contract.

Cats were decerebrated under deep anesthesia. Stimulating electrodes were applied to the popliteal nerve which was left uninjured from the center to the gastrocnemius muscle; another pair of stimulating electrodes was applied to the peroneal nerve in the same leg, cut distal to the point of stimulation; they were connected with separate coils. Thus the popliteal nerve could be stimulated with single break shocks before, during or after stimulation of the peroneal nerve by interrupted current. Stimulation of the peroneal nerve causes reflex inhibition of the gastrocnemius muscle; in some cases this is followed by rebound contraction. Non-polarizable electrodes applied to the gastrocnemius muscle were connected with a string galvanometer, and a muscle lever was arranged to record the contractions on a smoked drum.

In a large majority of tests submaximal stimuli caused larger contractions during reflex inhibition than during reflex excitation, whether in the form of decerebrate rigidity or post-inhibitory rebound or in the crossed extension reflex produced by pinching the opposite foot; and the greater the reflex excitation, the less the response to motor nerve stimulation. The action currents simultaneously recorded obeyed the same law and proved a more dependable criterion, because of the difficulty of comparing contractions starting from different base lines.

A small percentage of exceptions to the rule was found, and these may be explained as due either to accidental shifting of electrode contact, or to the occasional stimulation of a group of idle fibers at the same moment that another considerable group was responding reflexly.

The experiments do not seem to support the view that the neural discharge involved in decerebrate rigidity is fundamentally different from other forms of reflex excitation of muscles.

[1] Forbes and Rappleye: This Journal, 1917, xlii, 228

The effect of adrenalectomy upon the total metabolism of the cat. JOSEPH C. AUB, JOHN FORMAN and ELIZABETH M. BRIGHT

The metabolic rate of three adrenalectomized cats was determined. This was done by means of a Benedict unit apparatus and a small water-sealed copper box. All movements were recorded. The CO_2 and O_2 exchange was thus obtained, and the metabolic rates then calculated. The apparatus was repeatedly controlled by blank runs and alcohol checks, and all calculations were checked. Very careful basal rates were first obtained, with the animals in the post-absorptive state. Frequent observations were made and only the very quiet periods taken as controls.

The animals were operated by the posterior route, and the adrenals removed intact. There was a slight rise in the metabolic rate for some hours, and 48 hours after operation a sharp fall to about 25 per cent below normal. This remained until the animals were sacrificed, 5 days after operation. They were very weak at this time, but conscious and quite capable of walking and jumping from tables. One had a blood pressure of 106 mm. Hg.

The factors which had to be controlled, other than blood pressure and movements of the animal, were three:

1. The temperature of the cat was maintained by having it lie on a heated electric pad. By this method the animal regulated its own temperature and kept it slightly above the normal.

2. The reduced food intake which follows this operation was controlled by completely starving animals. The drop in metabolism was less than after adrenalectomy.

3. The operation was not the cause of the fall, because the metabolism fell only 12 per cent after control operation plus complete starvation.

The conclusion, therefore, seems justified that adrenalectomy in the cat causes a reduction of about 25 per cent in the basal metabolism. This occurs some hours after operation.

The relationship of the increase in blood sugar concentration to the specific dynamic action of glucose and to the specific dynamic action of adrenalin. WALTER M. BOOTHBY and IRENE SANDIFORD.

Forty-one experiments were made to determine the increase in the heat production, respiratory quotient and blood sugar concentration from the ingestion of 100 grams of glucose. Similarly twenty-two experiments were done to determine the specific dynamic action resulting from the subcutaneous injection of 0.5 cc. of adrenalin chloride (P. D. & Co.). The majority of the patients had hyperthyroidism although there was a sufficient number of non-hyperthyroid and of hypothyroid patients to show that there was no consistent percentile difference in the reaction from the glucose or adrenalin caused by variable amounts of active thyroxin in the body.

Curves were presented to show the characteristic reaction produced by glucose and by adrenalin chloride.

The average results for the two groups of experiments are as follows:

		GLUCOSE	ADRENALIN
B. M. R.	Before	+44	+34
	After	+57	+62
	Increase	13	28
Calories	Per cent increase	9	20
Blood sugar	Before	0.132	0.143
	After	0.271	0.196
	Increase	0.139	0.053
	Per cent increase	101	37
R. Q.	Before	0.77	0.77
	After	0.93	0.87
	Increase	0.16	0.10

There is, therefore, from the ingestion of glucose an increase in the heat production of 9 per cent for an increase in the blood sugar of 101 per cent; on the other hand, there is an increase in the heat production of 20 per cent as a result of the injection of adrenalin chloride with an increase of only 37 per cent in the blood sugar concentration.

We consider these experiments to be very strong evidence in favor of the theory tentatively suggested by us last year that adrenalin chloride, at least in the quantity here given, has a specific dynamic action on all the cells of the body causing them to metabolize more rapidly under its influence. This specific dynamic action is not due to the carbohydrate plethora coincidently produced by the adrenalin as has been the previous general conception of the reaction. The mobilization of sugar is a most interesting compensatory mechanism to render available an abundance of ready fuel to take care of the increased demand for it caused by the adrenalin. This assumption is further strengthened by the fact that adrenalin chloride produced a very pronounced rise in heat production in an essentially complete diabetic with hyperthyroidism in whom the administration of glucose caused practically no increase in the heat production, although there was a very marked increase in the blood sugar concentration.

Report on the daily analysis of outdoor air from November, 1919, to November, 1920. WALTER M. BOOTHBY and KATHLEEN SANDIFORD.

From November, 1919, to November, 1920, 974 air analyses were done, nearly equally distributed among 18 Haldanes and six analysts. The Haldane burets had been calibrated in duplicate with mercury and the analyses carried out according to the technic described by Boothby and Sandiford. The air was collected outside the windows of the top floor of a five-story building in the center of Rochester, Minnesota.

The average composition of outdoor air determined from this series of 974 analyses is as follows: Carbon dioxide 0.036 per cent; oxygen 20.927 per cent; nitrogen and other non-absorbable gases 79.037 per cent. These results agree quite closely with the two series previously reported from this laboratory: the first consisting of 349 analyses with an average CO_2 per cent of 0.037 and an average O_2 per cent of 20.930; the second consisting of 343 analyses with an average CO_2 per cent of 0.035 and an average O_2 per cent of 20.930. The 343 analyses of the second series are included in the present report of 974 analyses.

Throughout the year the CO_2 remains essentially unchanged and shows no seasonal variation. However, the weekly average of the oxygen per cent lies between 20.930 and 20.938 during the latter part of January and the months of February, March, April and the early part of May; during the remainder of the year the weekly average lies between 20.918 and 20.930 per cent. In general this variation can usually be seen in the plotted curves for each Haldane apparatus though the individual curves are more irregular than the average curve. On account of this slight irregularity we are not yet prepared to assert that the variation noted represents a seasonal change in the oxygen content of outdoor (city) air.

Specific dynamic action of thyroxin. HENRY S. PLUMMER and WALTER M. BOOTHBY.

The specific dynamic action produced by the intravenous injection of different amounts of thyroxin in 69 cases of myxedema or hypothyroidism of varying degrees of intensity is reported and characteristic curves shown. The average results may be summarized as as follows:

Increase in B. M. R. from intravenous injection of thyroxin

Increase per mgm.	2.8	Increase per mgm. per sq.m.	4.7
Average variation	0.7 = 25%	Average variation	1.1 = 23%
Largest plus variation	2.8 = 100%	Largest plus variation	2.9 = 60%
Largest minus variation	1.8 = 64%	Largest minus variation	2.9 = 60%

AVERAGE B. M. R.	VARIATION IN SPECIFIC DYNAMIC ACTION DEPENDING ON THE ORIGINAL LEVEL OF THE B. M. R.				VARIATION IN SPECIFIC DYNAMIC ACTION DEPENDING ON SIZE OF DOSE			
	Average dose	Increase per milligram	Average dose per square meter	Increase per milligram per square meter	Average dose	Increase per milligram	Average dose per square meter	Increase per milligram per square meter
Above to −14	8.7	3.3	5.7	5.0	4.8	3.5	3.6	5.0
−15 to −19	9.1	2.3	5.1	3.9	6.9	2.8	5.2	5.0
−20 to −24	7.3	2.9	4.6	4.6	8.8	2.9	7.0	5.2
−25 to −29	10.9	2.8	6.2	5.0	11.2	3.3	9.3	4.8
−30 to −34	14.8	2.9	9.2	4.9	16.0	2.6	11.5	2.7
−35 and below	15.5	3.0	8.6	5.1	24.0	1.6	13.2	3.0

As can be seen from the above data and the dynamic curves the effect of 1 mgm. of thyroxin given intravenously is an increase in the basal

metabolic rate of 2.8 points; therefore a 10 mgm. dose can be predicted to increase the metabolism from −40 per cent to −12 per cent. The error of prediction is of a slightly less magnitude if the dosage is based upon milligrams per square meter of body surface. The height of the metabolic reaction most frequently occurs on the eighth day. By means of small intravenous doses of thyroxin repeated at short intervals it is known that less than 1 mgm. daily is sufficient more than to replace any loss or destruction of thyroxin in the body, although the exact amount has not yet been definitely determined. However, by exterpolation of the descending part of the dynamic curve of thyroxin it can be estimated that the rate of loss or destruction of the thyroxin usually ranges between 0.2 and 0.4 mgm. daily in a myxedematous subject brought up to a normal basal metabolic rate; total metabolism rather than basal metabolism, however, probably governs the rate of thyroxin loss. From the thyroxin curves it can further be calculated that 12 to 14 mgm. of active thyroxin must be present in the body to maintain the basal metabolic rate at the normal level. Pathologic variations in the basal metabolic rate are due, at least in most instances, to either an increase or decrease in this quantity, thus explaining the characteristic and fundamental alterations in the metabolic rate found in hyperthyroidism and in hypothyroidism.

If thyroxin is given by mouth the height of the metabolic reaction is usually not as great nor as constant as when given intravenously, probably due to its incomplete absorption from the gastro-intestinal tract. Therefore the daily oral dosage necessary to maintain the metabolism at a normal level in a myxedematous person is distinctly larger than the calculated rate of elimination given above; the oral dosage is not far from 1.6 mgm. daily.

The above data include the experiments reported by H. S. Plummer at various times since 1917, and the present averages agree essentially with his earlier series. Thyroxin undoubtedly has a specific dynamic action increasing the metabolic rate in proportion to the quantity actively present in the body. Kendall has suggested the probability that its specific action lies in aiding oxidation by rendering more readily available nascent oxygen atoms, which agrees with the theory of Plummer that "the active agent of the thyroid gland is a catalyst that accelerates the rate of formation of a quantum of potential energy in the cells of the organism."

Nomographic charts for metabolic rate determinations. WALTER M. BOOTHBY and RAYMOND B. SANDIFORD.

A series of nomographic charts was presented together with simplified tables by which the computation of the metabolic rate (heat production) from the data obtained by the gasometer method of indirect calorimetry can be made with the elimination of practically all mathematics. The metabolic rate can be determined by their use in 3 to 4 minutes.

Vasomotor reactions of the nasal cavity and post-nasal space to chilling of the body surface. STUART MUDD, ALFRED GOLDMAN and SAMUEL B. GRANT.

In previous communications (Journ. Med. Res., 1919, xl, 53; Journ. Exper. Med., 1920, xxxii, 87) we have shown that chilling of the body surface causes reflex vasoconstriction and ischemia in the mucous membranes of the palate, tonsils and oropharynx. In the present study the same reaction has been found in the post-nasal space and nasal cavity. In the nasopharynx the ischemia caused by cutaneous chilling and the recovery of blood supply upon rewarming, the latter usually for some time at least incomplete, have been found to be closely similar to the reactions of the oropharynx. In the nasal cavity the reactions are qualitatively similar but quantitatively much more striking. With cutaneous chilling the temperature fall of the nasal mucosa surface, which is an index of local diminution of blood supply, has been found in some instances to be more than 6°C. Rewarming causes a sharp rise of temperature—indicating increase of the blood supply back toward normal—as does also inhalation of amyl nitrite.

Temperature changes (and these are indices of alterations of vasomotor tone) were followed by means of thermopiles held in each case in apposition with the skin or mucous surface by a properly shaped piece of galvanized iron wire. For the nasopharynx the wire was held between the closed teeth, arched over the dorsum of the tongue, and, with a short vertical arm, carried the thermopile tips up against the posterior nasopharyngeal wall. For the nasal cavity a straight wire bearing the thermopile was held in a metal groove, closed by a set screw and connecting through a double ball and socket joint to a fiber-board plate which was held between the teeth. The temperature changes were thus followed for various sites on the surface of the nasal septum, inferior and middle turbinates and inferior and middle meati.

The threshold of the vasoconstrictor reflex to the nasal and nasopharyngeal mucosa was found to be lower than that to the skin of the forehead. Merely unwrapping the subject in the cool room—temperature 14° to 18°C.—in a number of instances caused depression in mucosal temperature without affecting that of the skin.

In experiments in which the wires were introduced into the nasal cavity profuse discharge of clear mucus occurred, both from the side directly irritated and from the opposite side. The rhinorrhoea was little if at all affected by the diminution of blood supply and shrinkage of the nasal mucous membrane which occurred in reflex response to chilling of the body surface.

Discharge from the nose has been at most a rare occurrence in experiments in which the nasal mucosa was not directly irritated.

For relation of these reactions to infections of the nose and throat, see Journ. Lab. and Clin. Med., 1921, vi, 175.

Factors determining the duration of consecutive phases of the cardiac cycle. CARL J. WIGGERS.

In order to evaluate the primary effects of drugs on cardiac musculature and to separate the primary from the secondary effects produced in the heart as a result of a variety of experimental pathological conditions, it is necessary to study the reactions of the heart to changing venous return, changing arterial resistance and changes in rate. The effects of these influences on the cardiac discharge and intraventricular pressure curves have been studied by Patterson, Piper and Starling and by Straub and will also be reported upon by the writer in the near future. This communication deals with the effects on the temporal relations of different cardiac phases.

On the basis of pressure curves simultaneously recorded from the left auricle, left ventricle and aorta, it has been possible to subdivide the periods of systole and diastole into the following phases: Systole into *a*, an isometric contraction phase; *b*, a maximum ejection phase and *c*, a reduced ejection phase. Diastole into *d*, a protodiastolic phase; *e*, an isometric relaxation phase; *f*, a rapid inflow phase; *g*, a diastasis phase, and *h*, an auricular phase. The effects of various influences on the duration of these phases are indicated in the following table:

PHASES	INCREASED VENOUS RETURN	INCREASED PERIPHERAL RESISTANCE[1]	INCREASED AORTIC RESISTANCE[2]	NERVOUS VAGAL SLOWING[3]	CENTRAL VAGUS SLOWING[4]
Isometric	−(sl) or 0	+(sl) or 0	+(sl)	−(sl. T)	−(sl)
Maximum ejection	+(sl)	−	++	+(T)	− or 0
Reduced ejection	+	−−	−	+(T)	− or 0
Total systole	+	−	+	+	− or 0
Protodiastolic	0	0 or (sl)	−	0 or +(sl)	0
Isometric relaxation	0	0	+	0	0
Rapid inflow	0	0	0 or +(sl)	0	0
Diastasis	0	0	0	+	+

Abbreviations: sl, slight; T, temporary; +, increased; −, decreased; 0, no change. The interpretation of these changes will form the basis of a later report.

[1] Produced by reflex vasoconstriction.

[2] Produced by mechanical stenosis of thoracic aorta.

[3] Produced by stimulation of peripheral cut vagus.

[4] Produced by chemical action on medullary centers and associated with increased arterial resistance.

Observations on the pathological physiology of circulatory stasis in man. R. W. SCOTT.

The subjects for this study were individuals with circulatory stasis from heart disease. They were free from any renal, vascular or lung disease (pulmonary emphysema) as far as could be determined and were for the most part males between 25 and 40 years of age, with rheumatic myoearditis, mitral stenosis and auricular fibrillation.

Data were obtained during periods of decompensation and compared with those found a few days later when the circulation was much improved from digitalis medication.

Individuals with acute decompensation showed a marked sensitivity to inspired CO_2 as judged by the minute volume of respired air and the subjective sensations of distress. Several patients were much more distressed breathing 1.5 to 2 per cent CO_2 than they were with 5 per cent CO_2 48 hours after the administration of digitalis. The changes in pulmonary reserve as indicated by vital capacity determinations were not of sufficient magnitude to account for this difference in reaction to CO_2 before and after digitalis. Further study of this point indicated a diminished capacity for binding CO_2 accompanying circulatory stasis. The CO_2 tension of the blood as judged by the level at which equilibrium is reached between blood and lung air was consistently low in decompensated patients, likewise values for the total carbonate content below normal were found by a direct determination on both the arterial and venous plasma. The data from different individuals show that as a rule a certain parallelism exists between the degree of circulatory failure and the level to which the plasma CO_2 falls.

Although the diminished buffer value of the blood is to some extent responsible for the distress observed in decompensated patients while breathing low concentrations of CO_2, nevertheless it appears that other important factors are concerned. These are being studied but not sufficient data are at present available to warrant any definite conclusions.

In the type of cases studied there was little change in the oxygen content of the arterial blood before and after digitalis. Oxygen capacity and content determinations indicated that in acute decompensation the blood is normally saturated with oxygen in its passage through the lungs. Elderly heart patients with pulmonary emphysema, however, did show arterial oxygen unsaturation.

The oxygen content of the venous blood was definitely below the normal limit during decompensation. The blood appeared quite black when drawn (in sharp contrast with the bright red of the arterial blood). A venous O_2 content of 4 volumes per cent was found in a patient whose arterial blood contained 18 volumes per cent of oxygen.

It appears therefore that in uncomplicated cases of acute cardiac decompensation the buffer of the body fluids is diminished, as indicated by the low level of free and combined CO_2 and the marked sensitivity to low percentages of CO_2 in the inspired air. The arterial blood in most cases is normally saturated with oxygen in the lungs but it undergoes undue desaturation in the passage through the capillaries as indicated by the low oxygen content of the venous blood. The circulatory improvement occurring in some patients within 48 hours after adequate digitalis therapy is accompanied by a restoration of the blood alkali and the O_2 content of the venous blood to or near normal.

An explanation for the increased oxidation following the ingestion of fats, fatty acids and alcohols. W. E. Burge and J. Leichsenring.

The object of the present investigation was to determine if the introduction of fats, fatty acids and alcohols into the alimentary tract would

bring about an increase in catalase corresponding with the increase produced in oxidation by these materials.

The different kinds of alcohols, fats and fatty acids used are shown in table 1. After opening the abdominal wall these substances were introduced into the upper part of the small intestines. Catalase determinations were made before as well as at intervals after introducing the materials. The determinations were made by adding 1 cc. of blood to neutral hydrogen peroxide in a bottle and the amount of oxygen liberated in 10 minutes was taken as a measure of the catalase content of the 1 cc. of blood. By comparing the percentages it may be seen that practically all the substances used produced an increase in catalase. It may also be seen that the catalase of the liver blood increased more rapidly than that of the portal blood or the jugular. This is inter-

TABLE 1

ANIMALS	MATERIALS USED	NUMBER OF HOURS AFTER INTRODUCING MATERIAL	PERCENTAGE INCREASE IN THE BLOOD CATALASE
Dog 1	Butter	6	44
		24	69
		30	36
		48	4
Dog 2	Nucoa	2	30
		6	15
Dog 3	Lard	2	58
		6	36
Dog 4	Olive oil	1	5
		6	40
		12	36
		24	46
		30	3
Dog 5	Fish oil	1	37
		5	53
		12	56
		24	66
		30	16
Rabbit 1	Butter	6	12
		24	24
		30	0
Rabbit 2	Nucoa	2	7
		6	15
		24	26
		30	0
Rabbit 3	Lard	22	32
Rabbit 4	Olive oil	2	21
		6	10
		12	2

	PERCENTAGE INCREASE IN THE BLOOD CATALASE OF THE DOG		
	Liver blood	Portal blood	Jugular blood
60 minutes after introduction of methyl alcohol.....	22	16	6
30 minutes after introduction of ethyl alcohol.....	27	25	21
30 minutes after introduction of propyl alcohol.....	17	18	12
30 minutes after introduction of butyl alcohol.....	27	26	19
30 minutes after introduction of amyl alcohol.....	32	16	17
30 minutes after introduction of allyl alcohol.....	16	19	10
30 minutes after introduction of benzyl alcohol.....	37	13	18
30 minutes after introduction of glycerol alcohol.....	32	34	26
30 minutes after introduction of acetic acid.....	26	19	17
90 minutes after introduction of propionic acid.....	22	18	12
90 minutes after introduction of butyric acid.....	6	5	7
60 minutes after introduction of sodium butyrate.....	41	30	18
30 minutes after introduction of formic acid.....	2	1	3
30 minutes after introduction of sodium formate.....	36	20	10
60 minutes after introduction of valeric acid.....	4	3	1
60 minutes after introduction of sodium valerate.....	14	−1	3
60 minutes after introduction of stearic acid.....	1	−2	1
60 minutes after introduction of palmitic acid.....	−2	2	−1

preted to mean that the substances were stimulating the liver to an increased output of catalase.

The increase in oxidation after the ingestion of fats, fatty acids and alcohols in the alimentary tract is attributed to the increase in catalase brought about by the stimulation of the alimentary glands particularly the liver to an increased output of this enzyme.

The effect of starvation on the catalase content. W. E. BURGE and J. LEICHSENRING.

It is known that oxidation is decreased during starvation. The object of the present investigation was to determine if there was a corresponding decrease in catalase, an enzyme possessing the property of liberating oxygen from hydrogen peroxide. The reason for believing that there would be a decrease was that we had already found that whenever oxidation was increased or decreased there always occurred a corresponding increase or decrease in catalase.

The animals used were mice and Colorado potato beetles. Whole normal and starved mice as well as normal and starved beetles were vigorously macerated with a small amount of sand in a mortar for about 5 minutes. The catalase determinations were made by adding the macerated material to neutral hydrogen peroxide in a bottle and the amount of oxygen liberated in ten minutes was taken as the measure of the catalase content. The amount of the macerated material of the beetles was 0.5 gram while 1.0 gram of the mouse was used. It was found that if the material was macerated for more than 5 minutes it produced little or no increase in the amount of oxygen liberated.

By comparing in table 1 the amounts of oxygen liberated by 1 gram of the macerated normal mice with that of the mice starved for the different periods of time it may be seen that there was a great decrease in catalase during starvation, and that there was a great increase in catalase when the starved mice were given food. This increase in catalase on feeding is due to a stimulation of the alimentary glands, particularly the liver, to an increased output of this enzyme as we have shown in previous publications. The decrease in catalase during starvation is attributed to a decreased output of this enzyme from the alimentary glands.

By making a similar comparison for the adult beetles as well as the larvae it may be seen that the catalase content was decreased during starvation and increased after food.

The decreased oxidation during starvation is attributed to the decrease in catalase while the increased oxidation after food is attributed to an increase in catalase.

	Amounts of catalase measured in cc. of oxygen
Normal adult mice	610
24 hours starvation	593
72 hours starvation	412
96 hours starvation	231
24 hours after food	598
Normal adult beetles	1725
8 hours starvation	1600
16 hours starvation	975
208 hours starvation	150
4 hours after food	250
8 hours after food	350
16 hours after food	800
Normal full grown larvae	1600
16 hours starvation	1200
24 hours starvation	875
32 hours starvation	700
40 hours starvation	650
64 hours starvation	400
96 hours starvation	300
144 hours starvation	350

An explanation for the increased oxidation after fertilization during youth, and for its decrease in old age. W. E. BURGE and J. LEICHSENRING.

It is known that the respiratory metabolism or oxidation in the unfertilized egg is low, and that it is greatly increased after fertilization. It is also known that metabolism is low in the newly born, high during childhood and low after the onset of old age. We had already found that whatever increased metabolism in the body produced a corresponding increase in catalase, an enzyme possessing the property of liberating oxygen from hydrogen peroxide by stimulating the alimentary glands, particularly the liver, to an increased output of this enzyme.

The object of the present investigation was to determine if there was an increase or decrease in catalase corresponding with the variations in the intensity of oxidation enumerated above.

The animals used were mice and Colorado potato beetles. Whole mice as well as beetles were macerated vigorously with a small amount of sand in a mortar for about 5 minutes. The catalase determinations were made by adding the macerated material to neutral hydrogen peroxide in a bottle and the amount of oxygen liberated in 10 minutes was taken as a measure of the catalase content. The amount o the macerated material of the beetles was 0.5 gram while 1.0 gram of the mouse was used. It was found that if the material was macerated for more than 5 minutes it produced little or no increase in the amount of oxygen liberated.

The "unfertilized eggs" were those removed from the body cavity of the beetles and washed in normal salt. The "fertilized eggs" were collected shortly after they were laid from the leaves of the potato plant. "Very old beetles" were those that had been kept the whole summer. "Very old mice" were about 2 years old.

TABLE 1

The figures in the table represent amounts of oxygen liberated by 0.5 gram of macerated beetles and 1 gram of macerated mouse respectively from hydrogen peroxide in 10 minutes

COLORADO POTATO BEETLES	AMOUNTS OF CATALASE MEASURED IN CUBIC CENTIMETERS OF OXYGEN IN 10 MIN.	MICE	AMOUNTS OF CATALASE MEASURED IN CUBIC CENTIMETERS OF OXYGEN IN 10 MIN.
Unfertilized eggs	18	Newly born mice	164
Fertilized eggs	35	24 hour mice	190
Newly hatched larvae	280	48 hour mice	256
Quarter grown larvae	800	144 hour mice	288
Half grown larvae	1250	Quarter grown mice	435
Three-quarter grown larvae	1725	Half grown mice	582
Full grown larvae	1750	Mother mice	715
Pupae	1800	Very old mice	400
Adult beetles	1750		
Very old beetles	900		

By comparing in table 1 the amounts of oxygen liberated by the 0.5 gram of the Colorado beetle it may be seen that the fertilized eggs liberated more oxygen from the hydrogen peroxide than did the unfertilized ones and that the very old beetles liberated less oxygen than the adult beetles. The increase in catalase after fertilization is attributed to the stimulation of the egg by the spermatozoön to an increased output of the enzyme.

By making a similar comparison for the mice it may be seen that the newly born mice liberated less oxygen than the older mice, and that the mother mice or adults liberated more oxygen than the very old

mice. The low catalase content of the newly born and of the very old mice is attributed to the small output of catalase from the liver, while the high catalase content of the young vigorous adults is attributed to the large output of this enzyme from the liver.

The variations in the intensity of oxidation in the life cycle is attributed to the variations in the amounts of catalase.

Further observations on the results of feeding cotton seed meal and kernels.
ICIE G. MACY and N. M. ALTER.

In order to study the direct effect of cotton seed meal injury upon the animal organism, rabbits, guinea pigs, pigeons and albino mice have been fed on diets of cotton seed meal and kernels. Satisfactory consumption of these materials was obtained by moistening them with molasses. Roughage and vitamine content of the diet were furnished by cabbage in case of the rabbits, pigeons and guinea pigs. Mice received the same cotton seed products supplemented with butter fat and inorganic salts. In view of these supplemental additions, the diets cannot be criticized as being inadequate in respect to any of the essential components.

The experimental animals fed on cotton seed meal and cotton seed kernels declined in body weight and finally died. Necropsies were conducted and microscopical studies of all tissues were made. Macroscopically, there was an excess of fluid in the abdominal cavity; the liver, kidneys, and in many cases the lungs were congested to a greater or less extent. In over a third of the cases there was injury to the intestinal wall which ranged from congestion and small hemorrhages to extensive necrosis of the mucosa and deeper layers.

Microscopically, lesions were found most constantly in the kidneys; the glomeruli, the epithelium of the tubuli and the interstitial tissue being the points of injury. The injury to the glomeruli consisted of congestion and hemorrhage of the glomerulus itself; adhesion between the capsule and tuft; and an increase in the number of endothelial and wandering cells. In the tubuli there were degeneration and alteration of the epithelial cells of the lumen; sometimes casts were present. The interstitial tissue was the seat of scars consisting of fibroblasts and infiltration of lymphocytes and polymorphonuclear cells.

Control experiments, in which animals received daily the same quantity of an adequate control diet as that which the cotton seed meal animals consumed, demonstrated that death was not entirely due to starvation. None of these control animals died. In the cases of complete starvation already studied, the kidneys found under such conditions agreed only with the early lesions of cotton seed meal injury, that is, congestion. Advanced kidney lesions were not present.

In order to corroborate the above anatomical findings, chemical studies of blood and urine will be made.

The effect of various temperatures on blood catalase. O. O. STOLAND and LALIA WALLING.

The investigation was undertaken to determine whether blood catalase, claimed to be an enzyme concerned in metabolism, is influenced in its activity in vitro as are other enzymes of the animal body.

The catalytic action was measured in the usual way, a series of determinations being made on a given sample of blood subjecting the mixtures of hydrogen peroxide and blood to the desired temperature during the period of action. The catalytic action of defibrinated blood drawn from six dogs was determined at temperatures varying from −2°C. to 44°C. In every case the amount of oxygen released from the peroxide was greater when the mixtures were subjected to low temperatures and less when the action took place at high temperatures. The amount of oxygen released by the action of 0.5 cc. of blood at −2°C. was from 57 to 120 per cent greater than that released at 22°C. The catalytic action of dogs' blood at temperatures between −2°C. and 44°C. is practically inversely proportional to the temperature of the blood-peroxide mixture. Similar observations were made on blood drawn from two rabbits. These showed only a slight increase in activity at lower temperatures, the catalytic activity at −2°C. being only 13.7 to 17 per cent greater than at 22°C. Determinations made on six samples of human blood from five individuals showed a slight decrease in catalytic action at lower temperatures (−2°C. to 5°C.), but the action was practically uniform at temperatures from 15°C. to 43°C.

To determine at what temperatures catalase is destroyed blood was exposed to high and low temperatures for 20 minutes and the catalytic action determined at 22°C. It was found that blood drawn from six dogs lost practically all its catalytic activity when subjected to temperatures between 45°C. and 50°C. When the blood was exposed to temperatures between 0°C. and 45°C. very little if any loss in catalytic activity occurred. When exposed to temperatures from −10°C. to −14°C. the blood lost from 30 to 50 per cent of its catalytic action.

The results seem to indicate that catalase differs from other enzymes of the animal body in that it does not show its optimum activity at body temperature. The blood of some animals (dog, rabbit) has the greatest catalytic action at temperatures near 0°C. The blood catalase is nearly all destroyed at temperatures between 45°C. and 50°C. and is only partially destroyed at −14°C.

The diuretic action of pituitrin. O. O. STOLAND and J. H. KORB.

The earlier work on the action of the extract from the posterior lobe of the pituitary body lists it as diuretic, while more recent investigators report both diuretic and antidiuretic actions. This difference in opinion seems to be due mainly to the various methods employed.

It was our purpose in this investigation to devise a method which would permit of the collection of urine under conditions that were as near normal as possible; and to note whether either subcutaneous or

intravenous injection of pituitary extract would cause any quantitative variation as to either the volume or the nitrogenous content of the urine excreted.

In these experiments a bladder fistula was established in large, healthy, female dogs. In the course of a few weeks the fistula would heal until the opening was about the size of a lead pencil. The dog was then given a standard diet, placed in a sling and a special catheter introduced into the fistula. The urine was then drained from the bladder as rapidly as it was excreted into clean flasks which were packed in ice. Observations were started at 7 a. m. and ended at 7 p. m. Every 4 hours the flasks were emptied, volume taken and quantitative determinations of the total nitrogen, urea and ammonia were made. Determinations of the total nitrogen and urea in the blood were also made for the same periods.

Data were obtained on 5 days previous to treatment with pituitrin. The animals were then treated with 1 cc. subcutaneous or intravenous injection of pituitrin for 5 days and results on urine volume and nitrogenous content compared with control experiments. Following this observations were again made without the pituitrin injections.

In every case we obtained during the first 4-hour period after the injection of pituitrin an increase of 30 per cent in volume total nitrogen, urea and ammonia, in the second period a 50 per cent increase and in the third a 20 per cent increase. On the day following the injection of pituitrin the volume was about normal but the total nitrogen, urea and ammonia content was 20 per cent below normal the first 4-hour period, 10 per cent the second, and 5 per cent the third period. During the three 4-hour periods following the injection the total nitrogen and urea content of the blood were lowered about 40 per cent.

The above results seem to show conclusively that pituitrin acts as a stimulant to the kidney in that it produces such a marked secretion of urine that the nitrogenous content of the blood falls far below normal.

The gastrin theory put to physiological test. A. C. Ivy.

In this work a "two-gastric-pouch" animal was prepared, consisting of a pouch of the entire pyloric antrum[1] and a Pavlov pouch. Six of these animals have been prepared and have lived in good health as long as 3 months. Dextrose, N/10 HCl solution, gastric juice, peptone solution and meat extracts were applied to the mucous membrane of the pyloric pouch for a period of 1 to 2 hours without causing any stimulation of secretion in the Pavlov pouch. The Pavlov pouches in all six animals reacted normally to a standard meal of meat. The pyloric pouches secreted normally throughout the period of investigation and the mucosa of the pouch showed no histological changes. The absorption by the mucosa of the pouch was shown to be the same as by the mucosa of the pyloric antrum in situ, absorption of crystalloids (potassium iodide, strychnine, pilocarpine-hydrochloride) by the mucosa of the pyloric antrum being relatively very slow.

[1] For method see: Ivy: Arch. Int. Med., 1920, xxv, 6.

In the belief that Edkins and Tweedy[2] did not adequately control their experiments, the work of these investigators was repeated on a series of dogs and cats. It was found that there is an increased acidity of the normal saline solution that is put in the fundic chamber within the same limits as occurs when 15 cc. of meat juice are put in the pyloric chamber. The slight increase in acidity that occurs in both cases we believe to be due to the continuous secretion of the stomach.

TABLE 1

SIX DOGS (CONTROL), 50 CC. N. S. S. PLACED IN FUNDIC CHAMBER	SIX DOGS, 50 CC. N. S. S. PLACED IN FUNDIC CHAMBER AND 15 CC. MEAT EXTRACT PLACED IN PYLORIC CHAMBER	SIX CATS (CONTROL), 30 CC. N. S. S. PLACED IN FUNDIC CHAMBER	SIX CATS, 30 CC. N. S. S. PLACED IN FUNDIC CHAMBER AND 10 CC. MEAT EXTRACT IN PYLORIC CHAMBER
Acidity 0.01–0.08 per cent	Acidity 0.01–0.07 per cent	Acidity 0.05–0.09 per cent	Acidity 0.02–0.13 per cent

Not being able at present to find fault with our test, we are inclined to doubt the physiological significance of the gastrin theory.

Blood pressure and electrocardiographic changes in the dog during extreme oxygen want. CHAS. W. GREENE and N. C. GILBERT.

Before the last annual meeting we reported cases of marked changes in the electrocardiograms of normal young men taking the rebreather test for low oxygen. These showed a shift in the point of origin of the beat and in the character of conduction through the Purkinje system. In extreme cases the P wave entirely disappeared along with a marked slowing of the rate but with retention of the normal ventricular type of complex. We concluded then that the P wave was absent, not buried in the ventricular complex. Wilson has shown that under certain circumstances the electrocardiogram gives no evidence of the P wave, while the venogram shows the presence of the auricular contractions occurring simultaneously with the ventricular contractions. Two instances were reported by us showing great disturbances of the conduction with complete dissociation.

We report now an extreme case in which the details shown by the electrocardiogram are more concise. Lieut. A. was tested to 7.1 per cent oxygen, 28,000 feet elevation, gave normal circulatory and respiratory compensating responses in the pre-crisis period. At the crisis the heart rate was 136 per minute and respiration more than doubled the minute volume. The following changes in cardiac physiology appeared in rapid succession in an interval of about 28 seconds: *a*, The blood pressure sharply and abruptly fell with nerve muscle collapse ending in unconsciousness; *b*, The heart rate dropped from 136 to 44 per minute; *c*, The changes shown in the electrocardiogram are: First inversion of the P wave, then reversal to the post R position with ventricle-auricle sequence, and finally disappearance of the P wave alto-

[2] Edkins and Tweedy: Journ. Physiol., 1909, xxxviii, 263.

gether. Conduction measured by the P-R interval decreased at first by 10 per cent, which may mean a lower origin of beat, then became reversed and finally disappeared. The terminal reversed beats gave progressively longer R-P intervals indicative of diminishing rate of conduction. In this man the ventricular complexes were all of normal type until recovery.

We have used dogs under the rebreather test, with respiratory, blood pressure and electrocardiographic records to determine if possible the nature of the mechanism through which the slow rhythm and dissociated beats were induced. Dogs give pre-crisis responses perfectly comparable to those observed in man. At the breaking point and in the post-crisis there occur in rapid order, but overlapping in time, decrease in oxygen consumption, slowing and stopping of respiration, fall in blood pressure, slowing of the heart rate. In a typical case the slowing was from 156 to 44 per minute and less by more or less abrupt steps.

The electrocardiogram changes from the normal sequential type through various stages showing inverted and suppressed P waves, shortened P-R intervals, stages of partial or complete block, sometimes reversed rhythm, and ectopic beats.

If when the changes are advanced the vagus nerves are cut in succession, then partial recovery occurs when the first vagus is cut, either right or left, and complete recovery when the second vagus is cut. The heart at once beats in rapid rhythm and with normal sequential beats. In continued asphyxiation the normal beats progressively slow in rate and stop after 3 or 4 minutes. At any time during the post-crisis two or three breaths of normal air are followed by quick recovery.

Dioestrous changes in the mammary gland of the opossum and the diagnosis of pregnancy. CARL G. HARTMAN.

The Virginia opossum has a single breeding season a year; it is polyoestrous and ovulation is spontaneous. The dioestrous cycle is about 28 days.

A study of the correlated changes in the ovary, uterus and mammary gland is of peculiar interest. *a*, The opossum is one of the marsupials possessing no trace of a placenta; on phylogenetic grounds, therefore, one would not look to this organ for any important endocrine function having to do with reproduction. *b*, Pseudopregnancy is very marked in marsupials and the mammary gland hypertrophies for some days exactly as in pregnancy. Much growth of the mammary gland takes place, therefore, without any fetal influence. *c*, Growth in the mammary gland (both edema and hyperplasia) takes place in the opossum long before ovulation. It is, therefore, not initiated by the corpus luteum. That the ovary is, however, responsible oöphorectomy experiments amply prove. Hence the mammary hormone in proöestrum mus arise either *a*, from the follicles or *b*, from the interstitial tissue. Now the ripe follicles are 10 to 46 in number in each ovary and in section these organs appear like an Eutherian ovary in cystic degeneration. This fact speaks in favor of the secretory activity of the follicular epi-

thelium. Interstitial cells are, moreover, said to be absent from marsupial ovaries (Schaeffer, etc.); but I find in ovaries with ripe follicles cells containing fat granules in the theca folliculi and in small groups or isolated cells in the stroma. These are probably the interstitial cells. To ascribe to them the function of secreting the mammary hormone is in keeping with Steinach's results on transplantation of radiated ovaries.

Since the 11 to 13 mammary glands of the opossum are concentrated within a very restricted area in the pouch, it is possible by palpation alone to diagnose cyclic changes with great accuracy. The glands swell in proöestrum, increase to a maximum about 4 days after oestrus, then recede to a minimum in dioestrum to resume their swelling at the approach of another oestrous period. Five or 6 days after oestrus the pregnant and the pseudopregnant mammary glands cannot be distinguished either by palpation or by microscopical examination; after that time it is an easy matter to make the distinction: the pregnant gland grows slowly in thickness and turgidity, the pseudopregnant organ becomes flaccid and thin. The diagnosis of a case, whether pregnant or pseudopregnant, is then definite and unmistakable.

In the woman, also, there occurs an intermenstrual wave of swelling and subsidence of the breasts; and in pregnancy there is a progressive increase in the turgidity of the organs. The phenomena in opossum and in man appear to be homologous. Measurements of the volume of the human breast are now in progress in order to determine whether such data may be of value in the early diagnosis of pregnancy in man as in opossum.

The intestinal mechanism primarily stimulated by sodium carbonate. FREDERICK S. HAMMETT.

When the isolated duodenal segment of an unexcited, adult, male albino rat is suspended in 4 cc. of oxygenated Tyrode's solution at 39°C., the addition of 0.25 cc. of a 0.1 M. sodium carbonate solution causes it to shorten or contract. If the segment is then so treated by 1.0 per cent solution of cocaine that the usual rhythmical contractions are not abolished, the addition of the carbonate does not cause a shortening. When the segment has been treated with nicotine no interference with the sodium carbonate effect is observed. These phenomena are interpreted as evidence for the opinion that the extrinsic nerve fibers or endings in the isolated segment are the mechanism of the intestine that is primarily stimulated by the sodium carbonate, resulting in the shortening that is commonly obtained.

The quantitative measurement of static control in standing. W. R. MILES.

It is common to test the stability of a man's coördinating mechanism by observing roughly the amount of sway while the subject stands erect with eyes closed. The movements of the body may easily be registered in smoke if a helmet is worn, but such records are so complicated that the actual length of the path traced can hardly be measured;

therefore one must content himself by giving the extreme anteroposterior and lateral excursions as the score.

The apparatus described consists of a square frame adjustable in height and carrying at each corner a movement-adder. These four movement-adders operated by light cords and weights attached to the subject's helmet accumulate the total sway in the four directions, forward, backward, right and left. The device has minimal friction and is practically without noise. The start and end of the test period are definite. The score is read directly in millimeters and a graphic record is also provided.

Normal data are presented and this quantitative test is shown to be sensitive to the nervous condition of the patient.

The inhibitory effects of vagus stimulation on gastric motility in the turtle. Z. BERCOVITZ and F. T. ROGERS.

Intragastric pressure and the contractions of the stomach were studied by introducing a balloon into the stomach of decerebrate turtles. It was found that whereas electrical stimulation of the vagus nerve with the ordinary tetanizing current causes contraction of the stomach, stimulation intermittently at the rate of one per second causes relaxation of gastric tone and frequently cessation of spontaneous contractions in progress. This inhibitory effect is independent of the intensity of the stimulus, provided the rate of stimulation is rather slow.

Furthermore, it is found that motor effects do not follow a single stimulus, howsoever intense, applied to the vagus trunk but that about 20 to 30 stimuli are required to give a minimal contraction. It is suggested that this indicates a synapse between the vagus endings and the intragastric plexuses and summation of impulses is necessary to overcome this resistance. Repeated periods of stimulation of the vagus trunk with a tetanizing current at short intervals of time are followed by progressively weaker contractions and finally no motor response. This suggests a ready fatigue of the junctional tissues or the onset of refractory conditions in the gastric motor mechanism.

The relation of the cerebral hemispheres to the sympathetic nervous system. F. T. ROGERS.

It has been pointed out in a recent report that removal of the cerebral hemispheres of the pigeon leads to a permanent slight fall in arterial blood pressure. This suggested possible changes in the sympathetic nervous system other than the vasomotor. It has been found that electrical stimulation of the cerebral cortex has little effect on the smooth muscles of the feathers of birds but that stimulation of the areas in the base of the cerebral hemispheres causes prompt contraction of the muscles that flatten the feathers against the body. This is particularly easily demonstrated in birds under light ether anesthesia with fluffed feathers.

The old observation that removal of the hemispheres leads to characteristic erection of the feathers and this one, that stimulation leads to depression of feathers, indicate a functional tonic relationship between the pennamotor nerves and the basal regions of the cerebral hemispheres.

Tonus rhythms produced experimentally in the diaphragm muscle of the cat in situ. L. B. NICE and A. J. NEILL.

Oscillations in diaphragm muscle have been observed by a number of workers in dogs and rabbits during normal sleep and under anesthesia.[1] The cause for these oscillations is considered to be of central origin.[2]

We have noted these oscillations in urethanized dogs, rabbits, cats and decerebrate cats. They may appear from 1 to 7 hours after the urethane (2 grams per kilo of body weight) is administered by stomach. In an attempt to find whether they may not be due in part to changes in the irritability of the muscle itself, the following experiments were performed. Cats anesthetized with urethane (2 grams per kilo) were fastened back down on the animal board and simultaneous records of the respiration and blood pressure made. The former was recorded by attaching an S-shaped hook into the diaphragm about midway between the lateral chest wall and the central tendon of the diaphragm and a thread passed from it over a pulley to a writing lever as employed by Nice in former work.[3] The blood pressure was recorded from a femoral artery by means of a mercury manometer. After the diaphragm had shown oscillations, the brain of the animal was quickly pithed, the phrenic nerves cut and the peripheral end of one stimulated with make induction shocks at the rate of 120 per minute. Then artificial respiration was administered for about 5 minutes, after which a second series of stimuli was applied to the phrenic nerve and so on. Under our experimental procedure the diaphragm gave tonus rhythms similar to those obtained by Cannon and Nice and others[4] on the tibialis anticus muscle of the cat when the peripheral end of the cut sciatic nerve is stimulated. Evidence will be obtained on dogs and rabbits for comparison with the activity of the diaphragm of the cat.

Endocrinological studies of the prostate. D. I. MACHT.

The effect of feeding prostate gland desiccated and fresh, from various animals, to tadpoles was studied and it was found that prostate feeding hastens the metamorphosis of frog larvae and salamander larvae, but unlike the thyroid gland the prostate does not produce shrinkage of the animals; it indeed has a tendency to produce an increase in their size and weight.

A study of the effect of prostatic extracts on the contractions and tonicity of various genito-urinary organs was made. The excised uterus, fallopian tubes, bladder, ureter, vas deferens and seminal vesicles were examined in this connection by Macht and Matsumoto. The conclusions drawn indicate that the prostate has no particular bearing on the

[1] Mosso: Archiv. ital. de biol., 1886, vii, 48; ibid., 1903, xl, 43; also McLeod: Physiology and biochemistry in modern medicine, St. Louis, 1908, 370.

[2] McLeod, loc. cit.

[3] Nice: This Journal, 1914, xxxiii, 204; 1914, xxxiv, 326; xxxv, 194.

[4] Cannon and Nice: This Journal, 1913, xxxii, 55; Gruber: Ibid., 1914, xxxiii, 348 and 351; Cannon and Gruber: Ibid., 36.

contractions of the various organs, in general, and on the bladder in particular.

Experiments were conducted by Macht and Miss Beulah Wells on the effect of prostatic extracts on the coagulation of blood in vitro. It was found that various prostatic extracts tend to hasten the coagulation time and in many instances to a greater degree than the extracts of some other glands. A chemical examination seemed to show that this effect was not due to any specific prostatic constituent but due to kephalin.

Studies were made by Macht and William Bloom concerning the effect of the prostate on the intelligent behavior of albino rats in the circular maze. Rats were trained to solve the maze problem and then prostatectomized. Their subsequent behavior after prolonged rest was observed. In another series of experiments, rats were prostatectomized first and the rate of learning was studied after recovery from the operation. As a result of this elaborate investigation it was concluded that the internal secretion of the prostate bears no relation to the intelligent behavior or "mental efficiency" of the animals.

An inquiry is being conducted by the author into the innervation of the prostate gland through the study of the excised portion of the gland in vitro. The data so far in hand warrant the conclusion that the prostate in most animals is more richly supplied by nerve endings belonging to the true sympathetic system, than by those belonging to the sacral or parasympathetic system.

The investigations on prostate feeding to tadpoles and concerning the effect of prostatic extracts on the contractions of the genito-urinary organs have appeared in the Journal of Urology. The investigation concerning the effect of the prostate on behavior is in press in the same journal and the other two investigations will appear in the same publication, in due time.

Contributions to our knowledge of the center of gravity in man. PERCY M. DAWSON and CO-WORKERS.

I. Studies by Borelli's method by Alma C. Luessen and Irma E. Marohn: The subjects of this study were 50 men and 50 women whose weight and height showed the following characteristics:

	WEIGHT IN KILOS			HEIGHT IN CENTIMETERS		
	Men	Women	Both	Men	Women	Both
Average	65.88	59.38	62.11	173.32	163.49	168.40
Standard deviation	±5.227	±6.54	±6.773	±5.55	±7.594	±7.9

The center of gravity in the men was 56.18 per cent of the distance from soles of feet to crown of head; in women 55.44 per cent; in both sexes 55.81 per cent. The standard deviations in these three cases were respectively, +0.234, +1.09, +0.9554. The coefficients of corre-

lation with weight and height were 0.54 (men), −0.12 (women), 0.01 (both) and −0.45 (men), −0.05 (women), 0.14 (both) respectively. Curves of distribution have been made for both sexes. Effects of *a*, extension of arms above head, *b*, flexion of lower extremities, *c*, of both these procedures were observed. The first causes a greater change in the position of the center in men; second gives a more uniform change in women; third gives a change which is almost as great as the sum of the preceding two (maximum 10 per cent of body length).

II. Studies of the accuracy of Borelli's method by Marguerite I. Croskey and Hazel E. Wright: The subjects of this study were 13 women whose centers were determined five times with and five times without clothing. If we consider this to be equivalent to 5 observations on 26 subjects, the accuracy may be inferred by these figures: Maximum difference between largest and smallest determination 1.5 per cent of body length, minimum difference 0.1 per cent, average difference 0.6 per cent. On comparing the observations with and without clothing one finds that the maximum difference (due to clothes) is 0.8 per cent of the body length, minimum difference 0.0 per cent, average difference 0.216 per cent.

III. Studies by Haycraft's method by Dorothy Jean Patterson (under the direction of Ethel Ronzone): The subjects of this study were university students, 18 men and 24 women. Drawings were made showing the relation of the axes of rotation of the principal joints (shoulder, hip, knee, ankle) to the vertical passing through the center of gravity. Great variations were found, viz., +1.3 to −3.5, +3 to 0, +2 to −3.5 and 0 to −4 respectively (+ = joint in front of weight line, − = behind; the numerals are percentages of the body length). The average position of the ankle joint was the same for both sexes. The averages for the other joints were further posterior (minus) in men than in women.

Heat block in nerves. PERCY M. DAWSON and ELVIRA O. OSTLUND.

In 1908 Max Hafemann found that heating the sciatic of a frog to a temperature of 45° caused blocking of the sensory impulses originating from an electrical stimulus applied distally to the heated region while motor impulses due to stimulation applied proximally to the heated area were unaffected. In 1913–14 one of us (P. M. D.) repeated and confirmed Hafemann's results.

The present communication deals with the nerves of a warm-blooded animal (rabbit). The anesthesia was produced with urethane and chloral per os and ether. Respiration was recorded by side tube from trachea cannula and served as an index of effective sensory stimulation. The heating was accomplished by bathing the nerve in a stream of hot saline. At 46°–50° the sensory impulses became blocked while the motor impulses continued to pass through the heated area. This result is explained as in the case of the frog by the assumption that the sensory fibers are more easily damaged by heat. But with large nerves like the rabbit's sciatic a second possibility presents itself, namely, that

the sensory fibers form a sheath about and protect the motor. This seems unlikely but ought to be excluded by experimentation. Such experiments have not yet been performed.

Effect of spells of rest on physical efficiency. PERCY M. DAWSON and LUCY A. WALLRICH.

It has been shown by previous investigators that when physical work is "heavy" the output may be increased by interrupting the work with short intervals of rest. The writers sought to observe the character of the transition from light to heavy work. Two subjects were tested, the apparatus being a stationary bicycle with a weighted brake. The tests were *a*, continuous ride of one hour; *b*, interrupted ride, i.e., riding 10 minutes and resting 5 minutes alternately for 1 hour. With light weights the number of revolutions per hour was much greater with continuous riding but as the weights were increased this advantage of the continuous ride decreased rapidly. One subject beginning with a heavy weight performed many more revolutions with intermittent riding but as his strength and skill increased this advantage became entirely reversed so that at the end of this series the number of revolutions was much greater with continuous riding.

An examination of certain cardiovascular indices. PERCY M. DAWSON and FRANCES V. KUPPERMAN.

Among the indices which have been used clinically are Stone's "overload factor," $\frac{PP}{DP}$, normal limits 40–60; Tigerstedt's "coefficient," $\frac{PP}{SP}$, normal limits 25–35, and Barach's "S. D. R. index," (SP + DP) × PR, normal upper limit 20,000. These formulae are so unlike that which represents heart work, that if they are to be tested at all it must be by the empirical method of tentatively assuming them to be correct until they win our confidence or land us in obvious absurdity.

Accepting them at their alleged value and applying them to cases found in the literature, we were led to the following conclusions:— *1.* Better limits for the coefficient and factor in normal adults are 20–45 and 25–55 respectively; in children the limits of normality are still wider. In adults the index usually lies between 13,500 and 18,000. *2.* The effort of the heart and its waste per beat, also the energy expenditure per minute are more variable in children than in adults and on the whole are greater. *3.* Marathon runners with enlarged hearts expend more than the usual amount of effort in relation to their systolic output and of this effort more is wasted proportionally than usual. This condition is exaggerated after the race. *4.* Football players show a greater variability than normal persons as to waste per systole and expenditure of energy per minute but this variation decreases during the football season. On the whole these three items of expenditure are less than in the controls.

The capillary circulation in the cat's ear. D. R. HOOKER.

The demonstration was primarily intended to show the feasibility of using the preparation in student teaching. The animal was suitably anesthetized and the inner surface of the ear shaved, cleaned, dried and sealed to the flat surface of the animal holder with collodion. The area to be inspected was flooded with a drop of castor oil and illuminated with a 32 c. p. lamp. An ordinary, low-power microscope adapted by removal of the stage to fit over the animal board is sufficient to display the corpuscular flow in the capillaries and venules.

In many respects the preparation is superior to the frog for demonstrating the circulation to students. Obviously it is adapted to certain lines of research (see this Journal, 1920, liv, 30).

The hours of work in relation to quality of output. A. H. RYAN and P. S. FLORENCE.

In the three jobs studied, footpress, threading tube and grinding springs, there was an enormous difference in both the daily and the relative hour by hour percentages of scrap. These divergent results strongly indicate the need for some analysis and common classification of industrial operations. The principle employed has been to analyze the job in terms of the receptor stimulus and effector response. The footpress job, for example, involves, as regards spoiled work, only the visual receptor whereas in the other two jobs both the visual and deep receptors are used. The first job then employs single receptor while the latter two employ multiple receptors. Since the outflow for both receptors is along the same effector path both of these jobs may be considered as allied reflexes. However, there is this difference; in the threading tube operation both visual and deep receptors are stimulated simultaneously whereas in the grinding spring operation these receptors are stimulated successively, resulting in a delay after the visual stimulus.

In addition to the number of receptors we must take into account the quantitative value of the stimulus. This may be best expressed in terms of the liminal value for the given receptor. We may thus designate the value of the stimulus as 1, 2, 3, etc., depending upon whether it is just the liminal value or 2, 3, etc., times the liminal value. We have called this the fineness of discrimination. Of the jobs we studied, that in which the discriminations were finest for both receptors is the grinding springs; threading tube ranking next, and footpress last. In addition to the fineness of discrimination we must obviously take into account the number of sensory patterns for the given receptor. The character of these patterns may vary in spatial configuration, in time relations or in intensity. In these three jobs the number of patterns is low although in many jobs it is high.

On the effector side we may analyze the muscle group which reacts, the response lag, the percentage effective tension (obtained by dividing the tension produced by the absolute contractile force), the "tension-time," the rest dilution, including massed rest, rest in the operating cycle and total rest for the day, the number of discriminations for the

working period, etc. A more detailed consideration of the physiologic analysis of industrial operations will appear elsewhere.

This analysis reveals that our three jobs are vastly different from the physiological standpoint. Where a single receptor is employed with a relatively strong stimulus, that is the footpress job, the percentage of scrap is low and is practically uniform throughout the day. Where two receptors are employed, a rise in the percentage of scrap occurs toward the end of the spell, the highest 2-hourly period being the last 2 hours of the day; but of these latter two jobs the grinding spring differs in that there is delay interposed after the visual stimulus, and in that the discriminations are finer. In the latter job the percentage scrap for the day is highest.

Space does not permit of presentation of the detailed hour by hour study that has been made of the spoiled work in these jobs.

Further experimental removal of the sino-auricular node. J. A. E. EYSTER and WALTER J. MEEK.

Recent experiments concerning the influence of removal of the sino-auricular node in recovery animals on cardiac rhythm have tended to substantiate the provisional conclusions previously put forward by us, namely, that complete removal results in the permanent establishment of coronary sinus rhythm, usually after a variable period of frank auriculo-ventricular rhythm, and that partial removal in which not more than two-thirds of the node is excised, results in a return of sino-auricular rhythm after a variable period of auriculo-ventricular rhythm. Preceding the return of the normal rhythm in the latter instances, we have noted the occurrence of periods of auriculo-ventricular dissociation in several animals. Histological examination in these animals has shown that a portion of the node along the auricular border was intact, separated in large part from the intercaval regions by the incision. If conduction of the impulse from the sino-auricular node to the auriculo-ventricular node and the ventricles occurs by way of the right auricle, as ordinarily assumed, one is forced to explain the occurrence of auriculo-ventricular dissociation by an interruption of the conduction paths beyond the auricle. On the other hand, if conduction from the sino-auricular node to the right auricle and auriculo-ventricular node occurs by separate paths, the dissociation is explicable on the lesion actually produced and confirmed by histological examination in these animals. We regard this result as evidence therefore for the presence of such separate paths of conduction, and believe that the dissociation noted in these experiments was due to partial sino-ventricular heart block.

Experimental observations upon the ureters. GEORGE B. WISLOCKI and VINCENT J. O'CONOR.

After partial ligation of the ureter its lumen increases in diameter and its musculature hypertrophies. When an incompletely ligated ureter is examined several weeks or months after operation, spontaneous peristalsis and frequently antiperistalsis are encountered. The peristaltic

waves are always more vigorous, and occasionally more frequent, than those seen in the normal ureter. Vigorous antiperistaltic waves, if not spontaneously present, may be elicited by pinching. By the application of a crystal of barium chloride to the surface of the dilated ureter, a constriction ring is formed from which peristaltic waves proceed in both directions. This local effect of barium chloride upon the ureter was first observed by W. G. Penfield. This and other interesting observations upon hydro-ureters, made by him in experiments which antedate ours, were reported in the American Journal of Medical Sciences for July, 1920.

The lumen of the completely ligated ureter is somewhat larger than that of the partially ligated one. The musculature is also hypertrophied. The completely ligated ureter seldom shows any spontaneous peristaltic movements nor does it usually react to stimuli. When, however, part of the contained fluid is released by withdrawal through a needle puncture through the kidney substance, violent peristaltic and antiperistaltic movements commence, which are in no way distinguishable from those observed in the partially ligated ureter. Replacement of the removed fluid content immediately causes a cessation of all ureteral movement.

Bands of muscle from both partially and completely ligated ureters contract vigorously when suspended in warm, oxygenated Locke's solution. The action of drugs on these preparations can be readily studied.

Glass beads of small caliber are propelled down the dog's ureter without any difficulty by a series of peristaltic waves and are finally expelled into the bladder. They leave no trace of their former presence in the ureter. Beads of somewhat larger diameter require a longer period to traverse the ureter. They stimulate the ureteral musculature to prolonged peristaltic exertion before they are expelled. Neither a bead of this nor the preceding size obstructs the passage of peristaltic waves from pelvis to bladder. As a result of the passage of several such beads, the ureteral wall may become hypertrophied. Slightly larger beads become lodged in the lumen of the ureter, most commonly at the renal pelvis or the intramural segment. These cause moderate dilatation and hypertrophy of the ureteral wall above the point of obstruction. Vigorous peristaltic waves come down the hypertropied ureter from the renal pelvis, but invariably stop at the bead. Below the bead other peristaltic waves originate and proceed toward the bladder. Antiperistaltic waves have not been observed arising spontaneously at the point of obstruction, although they may be readily called forth by gently pinching the ureter just above the bead.

On the internal secretion of Sandstroem's glands, parathyroid hypofunction and eclampsia. ALDO C. MASSAGLIA.

Animals—dogs and cats—operated upon for removal of two or three parathyroids, if they live in normal conditions, have no nervous symptoms. This special state is called "latent parathyroid insufficiency." When there is in the circulation an increase of the toxic substances

which the parathyroids neutralize, the single parathyroid, or the two parathyroids which remain become unable completely to perform their function, and we have an auto-intoxication ending in tetanic symptoms. Therefore with an increase of determined poisons in animals in a state of latent parathyroid insufficiency, a resulting tetany will show what kind of poisons are neutralized by the parathyroids. The waste products were increased in the circulation by means of: *a*, pregnancy; *b*, an impairment of the function of the kidneys by means of progressive stenosis of the ureters and of the renal veins; *c*, a derangement of the liver caused by a progressive stenosis of the ductus choledochus or of the portal vein; or *d*, from phosphorus poisoning; *e*, muscular fatigue induced by forcing dogs to run for a long time in a treadmill; *f*, lead poisoning.

The study brought out the following facts: *1*, the parathyroids neutralize the poisons from pregnancy, from muscular fatigue and from the intestine; they do not neutralize phosphorus or lead poisoning. *2*. Parathyroid hypofunction—especially in pregnancy—produces an auto-intoxication which injures the kidneys and the liver. However, neither a renal nor a hepatic hypofunction will directly produce a parathyroid hypofunction. *3*. Parathyroid hypofunction in pregnancy produces a tetanic syndrome exactly similar to eclampsia; therefore parathyroid hypofunction can be one of the causes of eclampsia. This does not preclude the possibility of other etiological factors. This conception is supported not only by experiment, but also by the findings in several autopsies on eclamptic women which showed a lack of the normal number of Sandstroem's glands or severe lesions in the parathyroids.

In eclampsia caused by parathyroid hypofunction, prompt treatment with parathyroidin gives good results.

Observations on the spread of temperature changes in tissues. N. B. TAYLOR.

Deep and superficial temperatures were recorded simultaneously by means of thermo-electric couples composed of fine copper and constantine wires twisted together at either end. One junction of each couple was housed in a hypodermic needle, and the other placed in water, at room temperature, contained in a Dewar flask to ensure against abrupt temperature changes. Each couple was connected with a Leeds and Northrup precision potentiometer and an Ayrton-Mather dead beat galvanometer. The potentiometer was sensitive to potential differences of one microvolt, which upon calibration was found to represent temperature changes of $\frac{1}{10}$°C.

Running water was the medium whereby heat was applied to the skin. The water flowed by syphonage from a reservoir to a smaller insulated flask and thence by syphonage into the "applicator." This latter consisted of a glass tube 3 inches long by 1 inch in diameter, closed at its lower end by a diaphragm of rubber dam. The maintenance of fixed inflow and outflow levels ensured against changes in temperature consequent upon fluctuations in the velocity of the stream.

By means of a thermocouple placed within the applicator and in contact with the rubber diaphragm the temperature of the contents of the applicator could be determined at any time. It was found that this temperature remained practically constant throughout the experiment.

Normal temperatures. Rabbits were the subjects of all the experiments, an area of 2 inches in diameter having been cleared of fur by shaving. A series of experiments was first made to ascertain the relationship which the superficial temperature, as recorded by needle "A" inserted in the subcutaneous tissues, bore to the deep temperature as determined by needle "B" buried in the muscles of the thigh. In all cases the deep temperature was higher than the superficial and though this difference—the temperature gradient—was constant in a single experiment it varied in different experiments, the variations being due to elevations of the superficial temperature rather than to depressions of the deep temperature. Local applications of oil or water had a marked effect through the diminution or augmentation of heat loss.

Local applications of heat to the surface of the body. The deep needle was placed at varying depths in the muscles of the thigh. The temperature of the applicator as it lay upon the shaven skin was from 44°C. to 45°C. The temperature of the subcutaneous tissues, needle "A", rose to within 6°C. or less of the applied temperature. The deep temperature, needle "B," rose more slowly and did not reach so high a level. The greatest depth to which needle "B" was inserted in any experiment was 20 mm. from the surface of the applicator. In this case there was a rise of 1.5°C. when the temperature of the applicator was 44.2°C. Anesthetics were found to have no influence upon the spread of heat.

Spread of heat to the abdominal viscera. Needle "A" was placed in the subcutaneous tissues of the abdominal wall. Needle "B" was placed in the lumen of the bowel, the abdomen having been opened for this purpose and closed again with sutures. The precise situation of this needle was determined by post-mortem dissection. It was found that heat penetrated to a greater extent through the abdominal viscera than was the case with skeletal muscle. In one instance the heat penetrated to and raised the temperature of needle "B" 5.5°C. when the latter was placed within the lumen of the cecum and at a distance of 7.5 cm. from the surface of the applicator. The temperature of the latter was at 47.5°C.

In no case was the general body temperature raised by local applications of heat.

A quantitative study of the effects of magnesium chloride on nerve. ESTHER GREISHEIMER and C. E. SHEPARD.

During the past three months we have been studying the effects of magnesium chloride on the sciatic nerve of the frog. The method used was the same as that described in an earlier paper (This Journal, xlix, 497). The $MgCl_2$ was recrystallized four times from water which had been redistilled from $Kmno_4$. The recrystallized salt gave negative

tests for Ca, NH_4 salts, Ba, heavy metals, PO_4 and SO_4. The solution depressed the freezing point 0.44°C.

The relative rate of decrease of conductivity was determined by noting the distance between the coils necessary to produce a minimal response of the muscle at intervals. One hundred experiments were done with the magnesium chloride. The distance between the coils at 30-minute intervals is indicated in the following table.

$MgCl_2$

Time in hours	*Distance in centimeters*
Initial	30.5
0.5	27.7
1.0	27.2
1.5	29.0
2.0	22.6
2.5	21.6
3.0	19.5
3.5	16.0
4.0	15.3
4.5	14.9
5.0	12.7
6.0	12.7
6.5	12.5
7.0	11.9
8.0	10.9
9.0	11.3
10.0	10.8
20.0	8.6

It will be noted that there is a gradual fall in conductivity during the first hour. At 1½ hours the conductivity was invariably increased, and after this it decreased steadily for 4 or 5 hours—then remained almost at the same point for the next 15 hours.

The following table shows the results, which were obtained with twelve controls in Ringer's solution.

Ringer's Solution

Time in hours	*Distance in centimeters*
Initial	31.5
1.0	34.8
2.0	33.8
3.0	32.7
4.0	31.8
5.0	32.2
6.0	31.7
7.0	31.6
10 0	30.0
20.0	29.5

This table shows that the conductivity in Ringer's solution remained almost constant during the 20-hour period.

These are only comparative results, but they show that an effort is being made to make the investigations quantitative. We are hoping to continue the work, using a standardized coil. Some attempts have

been made to use a condenser discharge for a stimulus, and innumerable difficulties have been met. We are especially anxious to get in touch with investigators who have tried the condenser discharges, and to profit by their experiences in our future studies.

It was supposed that a marked depressing effect would be obtained with $MgCl_2$—but certainly, the results of the one hundred experiments already performed indicate that the action of this salt is not strikingly different from the action of other salts as KCl, RbCl and $CaCl_2$.